



1983

An Anatomical, Electrophysiological, and Behavioral Analysis of Cortical Efferent Plasticity in the Rat

Gwendolyn Kartje-Tillotson
Loyola University Chicago

Follow this and additional works at: https://ecommons.luc.edu/luc_diss

 Part of the [Anatomy Commons](#)

Recommended Citation

Kartje-Tillotson, Gwendolyn, "An Anatomical, Electrophysiological, and Behavioral Analysis of Cortical Efferent Plasticity in the Rat" (1983). *Dissertations*. 2162.

https://ecommons.luc.edu/luc_diss/2162

This Dissertation is brought to you for free and open access by the Theses and Dissertations at Loyola eCommons. It has been accepted for inclusion in Dissertations by an authorized administrator of Loyola eCommons. For more information, please contact ecommons@luc.edu.



This work is licensed under a [Creative Commons Attribution-Noncommercial-No Derivative Works 3.0 License](#).
Copyright © 1983 Gwendolyn Kartje-Tillotson

AN ANATOMICAL, ELECTROPHYSIOLOGICAL, AND BEHAVIORAL ANALYSIS OF
CORTICAL EFFERENT PLASTICITY IN THE RAT

BY

Gwendolyn Kartje-Tillotson

A Dissertation Submitted to the Faculty of the Graduate School
of Loyola University of Chicago in Partial Fulfillment
of the Requirements for the Degree of
Doctor of Philosophy

December

1983

DEDICATION

To Jonathan

ACKNOWLEDGMENTS

I would like to express my gratitude to Dr. Anthony J. Castro for his expert advice and guidance which made this work possible.

Sincere appreciation is extended to the members of my dissertation committee who were extremely helpful in their comments and criticisms, with a special thanks to Dr. E. J. Neafsey who willingly gave of his time to assist in my work.

I would also like to thank the faculty members of the Department of Anatomy, the graduate students, and the staff whose helpful suggestions contributed significantly to this work.

VITA

The author, Gwendolyn Kartje-Tillotson, was born on February 14, 1955 in Berwyn, Illinois.

In 1973 she graduated from Riverside-Brookfield High School in Riverside, Illinois. In September, 1973 she entered Northern Illinois University in Dekalb, Illinois, and in December, 1976 she graduated with a Bachelor of Science degree in Biology. She began her graduate studies in the Department of Anatomy at Loyola University Stritch School of Medicine, Maywood, Illinois, in July, 1977. She held a Basic Science Fellowship and taught gross anatomy, histology and neuroscience courses. In July, 1979 she became a Research Assistant on a grant from the National Institutes of Health. In 1980 she was elected into the Society of Sigma Xi and in 1981 she became a member of the Society for Neuroscience.

In June, 1983 she will begin a post-doctoral fellowship in the Department of Anatomy at Loyola University Stritch School of Medicine under the supervision of Dr. A.J. Castro.

The author is married to Stephen Tillotson and has one son, Jonathan Tillotson.

TABLE OF CONTENTS

DEDICATION. ii

ACKNOWLEDGEMENTS iii

VITA iv

LIST OF FIGURES vii

INTRODUCTION. 1

BACKGROUND. 5

 Plasticity Overview 5

 Cortical Efferent Plasticity. 6

 Recovery of Function 10

 Corticospinal Projection - Origin and Terminations 16

 Corticospinal Tract - Function 20

 Corticopontine Projection - Origin and Terminations 22

EXPERIMENTS. 28

 Expt. I. An Anatomical Investigation of the
 Topography of Anomalous Corticopontine and
 Corticospinal Projections. 28

 Abstract. 29

 Introduction. 30

 Materials and Methods 32

 Results 37

 Discussion. 42

 Expt. II. Electrophysiological Analysis of Motor
 Cortical Plasticity After Cortical Lesions in
 Newborn Rats 75

 Abstract. 76

 Introduction. 77

 Materials and Methods 79

 Results 84

 Discussion. 87

Expt. III. Limb Preference After Unilateral Pyramidotomy in Adult and Neonatal Rats.	100
Abstract.	101
Introduction.	102
Materials and Methods	104
Results	107
Discussion.	109
GENERAL DISCUSSION.	120
SUMMARY	126
BIBLIOGRAPHY.	128
APPENDIX A. Microstimulation Technique.	149

LIST OF FIGURES

Figures

Expt. I.

1. Principle nuclei of the basilar pontine gray 52
2. Cortical lesion and injection sites. 54
3. Distribution of normal forelimb motor corticopontine fibers. 56
4. Photomicrographs of forelimb motor corticopontine terminations. 58
5. Distribution of normal hindlimb motor corticopontine fibers. 60
6. Photomicrographs of hindlimb motor corticopontine terminations. 62
7. Topography of normal corticopontine fibers. 64
8. Topography of corticopontine fibers following neonatal SMC lesion. 66
9. Photomicrographs of aberrant corticopontine fibers. . . 68
10. Distribution of normal forelimb motor corticospinal fibers 70
11. Distribution of forelimb motor corticospinal fibers following neonatal SMC lesion 72
12. Photomicrographs of aberrant corticospinal fibers. . . . 74

Expt. II.

1. Extent of cortical lesion sites. 93
2. Photomicrographs of cortical lesion sites. 95
3. Cortical microstimulation maps. 97
4. Forelimb responses following microstimulation. 99

Expt. III.

1. Limb preference testing scores for adult pyramidotomies.	115
2. Photomicrographs of pyramidal tract lesions.117
3. Limb preference testing scores for neonatal pyramidotomies.119

APPENDIX

1. Microstimulation circuit.	151
--------------------------------------	-----

INTRODUCTION

Neuroanatomical plasticity is defined as the formation of anomalous neural connections in response to central nervous system (CNS) injury. This morphological alteration of CNS pathways is a well-recognized phenomenon observed throughout all levels of the neuraxis (see Cotman, 1978 and Flohr and Precht, 1981 for reviews). Although anomalous neuronal growth following injury to the adult CNS has been well-documented (see Cotman, et al., 1981), plasticity seems much more prevalent after brain damage in the immature animal, often resulting in the re-direction of CNS projections (Schneider, 1970; Hicks and D'Amato, 1970; Nah, et al., 1980).

Anatomical reports of aberrant cortical efferent pathways found after cerebral cortical lesions in newborn rats are particularly relevant to this dissertation. Specifically, after unilateral sensorimotor cortical (SMC) lesions in neonatal rats, cortical projections to the basilar pontine nuclei originating from the opposite unablated SMC, and which primarily distribute ipsilaterally in normal animals, demonstrate an increase in crossed projections to the contralateral pontine gray (PG) (Leong and Lund, 1973; Castro and Mihailoff, 1983). Similarly, the formation of anomalous ipsilateral

corticospinal fibers also occurs after unilateral pyramidotomy in newborn rats (Castro, 1978) and hamsters (Kalil and Reh, 1979). Further investigations at the electron microscopic level demonstrated structurally normal synapses associated with the anomalous corticopontine and corticospinal fibers (McClung and Castro, 1975; Leong, 1976a; Mihailoff and Castro, 1981).

Several clinical and experimental studies indicate that subjects sustaining brain injury at a young age demonstrate greater functional recovery when compared to subjects with similar brain damage sustained as adults (Kennard, 1942; Teuber, 1971; Stewart and Riesen, 1972; Milner, 1974), although exceptions to this "Kennard principle" have been reported and discussed (Goldman, 1974; Schneider, 1979). The increased capacity of the immature brain to form anomalous connections has led several investigators to suggest that neuronal plasticity may constitute the anatomical substrate responsible for recovery of function (Devor, 1975; Labar, et al., 1981; Neumann, et al., 1982).

Accordingly, this dissertation was undertaken to investigate further the functional implications of anomalous corticopontine and corticospinal projections. Experiments were conducted along three methodological approaches:

Anatomical

To attribute a positive functional role for anomalous pathways implies the formation of new axonal connections in an ordered, precise way as opposed to random, non-specific growth. To pursue this

implication the topographic distribution of anomalous corticopontine and corticospinal pathways was examined using two anterograde tracing techniques combined in individual animals. The results from this study demonstrated that the aberrant cortical efferent fibers do indeed distribute in a precise, somatotopic manner into functionally appropriate zones.

Physiological

Since electrical stimulation of the motor cortex evokes low threshold movements of contralateral limbs which are mediated primarily by crossed corticospinal fibers, the presence of aberrant ipsilateral fibers, if functional, might be expected to mediate low threshold movements of ipsilateral limbs. Low threshold, cortically evoked ipsilateral limb movements were indeed observed in adult rats that sustained neonatal, but not adult, unilateral SMC lesions. This study therefore suggests that anomalous cortico-efferent pathways are electrophysiologically active.

Behavioral

Using the behavioral measure of limb preference the possibility of recovery of function in animals sustaining neonatal pyramidal tract lesions as compared to animals given similar lesions as adults was evaluated. This study attempted to correlate the aberrant ipsilateral corticospinal tract, which develops after neonatal pyramidotomy, with functional sparing. The results from this investigation demonstrated that animals with neonatal lesions did not differ from those sustaining adult lesions in terms of the behavioral task measured.

Although no correlation between anomalous pathways and sparing of function was observed, further behavioral tests are needed before final conclusions can be drawn.

BACKGROUND

Plasticity overview

Until recent studies, particularly of the last decade, the mammalian central nervous system (CNS) was generally believed to be a rigidly arranged structure in that the only anatomical changes thought to occur were degenerative in nature resulting from advancing age, disease, or injury. The concept of inflexible CNS connections is especially relevant when considering patients suffering from damage to the brain or particularly of the spinal cord, where anatomical repair, and therefore possible functional recovery, was generally assumed to be minimal. The classic study by Liu and Chambers in 1958 challenged these views by demonstrating that the mammalian CNS was capable of altering its connections in response to injury. They found that dorsal root fibers of adult cats will "sprout", or increase their terminal density, in response to removal of other dorsal roots, or in response to the interruption of corticospinal fibers. Using adult rats, Goodman and Horel (1966) subsequently demonstrated the sprouting of optic tract axons to the lateral geniculate nucleus and pretectum in response to visual cortical lesions. Raisman (1969), using the electron microscope, reported plasticity in the septal nucleus of adult rats. The two main afferent inputs to this nucleus, the fimbria

of the same septal neurons; the fibers in the fimbria terminate primarily on dendrites, while the axons in the medial forebrain bundle synapse on the soma of these cells. After damaging the fimbria, fibers in the medial forebrain bundle formed new synapses on dendritic sites vacated by the fimbrial lesion, and in another set of experiments, following damage to the medial forebrain bundle, axons in the fimbria sprouted new terminals on the deafferented cell bodies of the septal neurons. Therefore, selective lesions resulted in a reorganization of the afferent inputs to the septum, with the intact fibers sprouting into vacated synaptic space. Since the pioneering studies cited above, CNS remodelling has been shown in virtually all systems including motor, somatosensory, visual, auditory, olfactory, and limbic systems (see Cotman, 1978; Lund, 1978; Tsukahara, 1981; and Flohr and Precht, 1981 for reviews).

Cortical efferent plasticity

Anatomical studies of the plasticity of cortico-efferent pathways have shown that following unilateral cortical lesions in newborn animals the spared, unablated hemisphere forms anomalous connections with the spinal cord as well as various brain stem regions. The rodent corticospinal tract, generally considered a completely crossed pathway (Brown, 1971), develops an aberrant ipsilateral component which distributes to the ipsilateral spinal cord gray matter (Hicks and D'Amato, 1970; Leong and Lund, 1973; Castro, 1975). Furthermore, electron microscopic studies demonstrated

seemingly functional synapses associated with this tract (McClung and Castro, 1975; Leong, 1976b). Neonatal unilateral pyramidotomy in the rat (Castro, 1978a) and hamster (Kalil and Reh, 1979) also results in an ipsilateral corticospinal tract, demonstrating that this aberrant pathway develops specifically in response to corticospinal tract ablation and is not dependent upon more generalized cortical lesions. In addition to projections to the spinal cord, anomalous cortico-efferent fibers were found to the reticular formation, dorsal column nuclei, and trigeminal complex (Hicks and D'Amato, 1970; Leong and Lund, 1973) as well as the tectum (Leong and Lund, 1973; Leong, 1976b), the pretectal region and the nucleus of Bischoff (Leong, 1976b).

The corticopontine projection, which is primarily an ipsilateral pathway, also displays altered projections following unilateral neonatal sensorimotor cortical lesions in rats. An anomalous increase of crossed corticopontine fibers appears to innervate areas deprived of their normal inputs after neonatal cortical lesions (Leong and Lund, 1973; Mihailoff and Castro, 1981; Castro and Mihailoff, 1983). Electron microscopic study indicates that these sprouted axons form structurally normal synapses (Mihailoff and Castro, 1981).

Hemicerebellectomy in newborn rats also causes an alteration of corticopontine projections which is attributed to the loss of cells in the contralateral pontine gray following such lesions. Corticopontine fibers which would normally terminate within the atrophied pons

abnormally cross to the opposite side as though redirected into the intact pons (Leong, 1977; Leong, 1980; Castro and Mihailoff, 1983). Combining neonatal hemicerebellar with ipsilateral neonatal sensorimotor cortical lesions demonstrated an increase in corticopontine sprouting which was denser than observed in animals with single lesions (Castro and Mihailoff, 1983). Also, corticopontine plasticity appears to be specific in that no alteration in the distribution of sensorimotor-pontine fibers was observed after neonatal occipital cortical lesions, nor was remodeling found in the reverse lesion sequence, i.e., there was no apparent redistribution of occipital-pontine fibers after neonatal sensorimotor cortical lesions. Furthermore, unilateral occipital cortical ablations in the newborn rat resulted in no change in the projection pattern of occipital-pontine fibers from the intact hemisphere (Castro and Mihailoff, 1983).

Additional examples of cortico-efferent plasticity have been reported after neonatal unilateral cortical destruction in both rats (Nah and Leong, 1976a) and cats (Sonnier, 1982). Using both anterograde degeneration and autoradiographic tracing techniques, aberrant contralateral projections to the red nucleus originating from the intact cortex were observed. Ultrastructural studies in rats confirm the existence of morphologically functional synapses related to this anomalous pathway (Nah and Leong, 1976b).

Studies of the red nucleus in the adult cat also demonstrate the remodeling of corticorubral fibers. In normal animals,

corticorubral afferents terminate on distal dendrites whereas cerebellar inputs terminate on proximal dendrites and cell soma (Tsukahara and Kosaka, 1968). However, after cerebellar lesions, cortical inputs appeared to reinnervate vacated sites by synapsing on proximal dendrites and cell soma (Nakamura, et al., 1974; Murakami, et al., 1982; Tolbert, et al., 1982). These findings were corroborated by electrophysiological studies in which corticorubral stimulation evoked EPSPs with faster rise times and larger amplitudes than are normally found in the intact animal (Tsukahara, et al., 1974, 1975; Murakami, et al., 1977a,b).

Further electrophysiological studies demonstrate that corticorubral synapses in the adult cat will remodel under conditions other than partial denervation. After cross-innervation of forelimb flexor and extensor nerves by surgically redirecting peripheral nerves, a new fast-rising component in the unitary corticorubral EPSPs appeared which suggests the formation of functional synapses on the proximal portion of rubral neurons (Tsukahara and Fujito, 1976; Tsukahara, et al., 1982; Fujito, et al., 1982). The apparent ability of the CNS to reorganize synaptic connections in the absence of lesions lends support to the concept of the CNS as a continually changing, dynamic structure.

Recent studies utilizing the retrograde transport of HRP have demonstrated an anomalous contralateral corticothalamic projection following unilateral cortical ablation in adult (Pritzel and Huston, 1981) and infant (Neumann, et al., 1982) rats. This appearance of

this aberrant pathway was correlated with the functional recovery from lesion induced behavioral asymmetries, i.e., the cessation of spontaneous turning behavior.

A particularly relevant study in primates (Goldman, 1978) describes the development of an aberrant cortical projection to the basal ganglia following unilateral removal of the prefrontal cortex in fetal monkeys. The evidence of structural rearrangement in the primate brain after early lesions supports the view that similar neuroanatomical plasticity may also occur in humans (Raisman, 1978).

Recovery of function

Various studies have demonstrated that animals sustaining brain lesions as infants recover better than mature animals receiving similar lesions. The influential investigations of Kennard (1936, 1938, 1940, 1942) demonstrated that monkeys sustaining motor cortical lesions in infancy were much less impaired on various motor tasks than monkeys with similar lesions sustained later in life. Further studies reported that animals with early cortical lesions performed better than adult lesion animals on delayed response tasks (Tucker and Kling, 1967; Kolb and Nonneman, 1978), on sensory discrimination problems (Benjamin and Thompson, 1959), on sensory-motor tasks (Stewart and Riesen, 1972), on solving complex mazes (Tsang, 1937), and on other higher order perceptual learning tasks (Harlow, et al., 1968). Similar studies involving human subjects have reported sparing of

function in patients with early brain injury as compared to injury sustained later in life (Milner, 1974; and reviewed by Teuber, 1970).

In contrast to these studies, other investigators have demonstrated little sparing of function following neonatal brain damage (Isaacson, 1975; Passingham, et al., 1978; Schneider, 1979; Gramsbergen, 1981; Prendergast, et al., 1982; and see Johnson and Almlil, 1978 and St. James-Roberts, 1981 for reviews). As an explanation for such discrepancies in the literature, Goldman (1974) suggests that the effects of brain damage on young animals may be related to the degree of functional maturity of the brain region under investigation and the age at time of testing. Her studies have shown that ablation of the dorsolateral frontal cortex in neonatal monkeys did not affect performance on a delayed response task when animals were tested at one year of age. However, severe deficits were observed when the monkeys were retested when two years old. Similar delays in the appearance of deficits have been reported in studies of brain damaged children (Teuber and Rudel, 1962; Lenneberg, 1968). Goldman also found that removal of the orbital prefrontal region in infant monkeys caused impairments on a delayed alteration task when animals were tested at one year of age, but no deficits were observed when these animals were retested at 2 years of age. Her studies therefore indicate that the locus of damage and time of testing are important factors in assessing recovery of function.

From these studies, it is clear that the "Kennard principle" of greater recovery of function following early brain damage is not

without exception. However, studies demonstrating recovery have often suggested that the apparent sparing may correlate with the increased capacity for anatomical reorganization in the developing nervous system, in comparison to the relatively less flexible mature nervous system. The concept of altered neuronal connections after early lesions was first proposed by Kennard in explanation of the functional recovery observed in neonatally ablated monkeys, but the idea received little attention due to the lack of anatomical evidence. More recent studies have attempted to correlate spared behaviors with anomalous pathways. Hicks and D'Amato (1970) showed that rats sustaining cortical lesions at maturity developed a slight impairment in the stride component of running, whereas adults that received neonatal lesions demonstrated sparing of this function. They suggested that the uncrossed corticospinal tract which develops after the neonatal lesions, but not after adult lesions, provided the bilateral innervation essential for normal stride. Further studies of limb preference in adult rats after neonatal cortical lesions reported a tendency to use the limb corresponding to the aberrant corticospinal tract, and this preference was not found after adult cortical lesions (Castro, 1977).

The olfactory system also appears to remodel following neonatal lesions (Devor, 1975), and this remodelling has also been correlated with functional recovery. Bilateral lesion of the lateral olfactory tract in adult hamsters effectively eliminates mating behavior, which is dependent on the sense of smell, whereas the same lesions in 3 day

old hamsters result in considerable sparing of mating behavior later in life. This sparing is correlated with the ability of axons from the olfactory bulb to sprout new terminals and reinnervate olfactory cortical tissue distal to the lesion.

In studies of the rodent visual system, bilateral removal of visual cortex in neonatal hamsters resulted in an alteration of retinocollicular fibers which redistributed to the deeper layers of the superior colliculus as well as maintaining their normal projection to the superficial layers (Schneider, 1970). This rerouting of axons was not observed after similar cortical lesions in adults. Behavioral testing found that animals sustaining lesions at early ages could learn striped pattern discriminations, while animals ablated as adults failed to learn the task. Furthermore, bilateral damage to the superficial layers of the superior colliculus in newborn hamsters caused a rerouting of retinal fibers to the undamaged, deeper layers of the colliculus as well as to the pretectal region, the lateral posterior nucleus of the thalamus, and the ventral nucleus of the lateral geniculate body (Schneider, 1973). Animals with this aberrant neural circuitry displayed sparing of visually guided behavior in their ability to orient towards a food reward. It was postulated that the anomalous projection to the deep layers of the colliculus was responsible for the preservation of the orienting capacity (Schneider, 1973, 1979). However, a recent electrophysiological study disputes this hypothesis (Finlay and Cairns, 1981). Other experiments indicated that unilateral visual tectal lesion at an early age results

in a further anomalous connection. Retinotectal fibers destined for the damaged colliculus recrossed the midline and terminated in the superficial layers of the opposite intact colliculus (Schneider, 1973). These animals displayed unusual visually guided behavior in that presentation of sunflower seeds in the upper visual field resulted in head turning away from the stimulus instead of towards it. The axons that anomalously recrossed to the opposite side of the brain were apparently mediating this maladaptive type of behavior since transection of this recrossing bundle of fibers in adulthood abolished "wrong way" turning (Schneider, 1979). Therefore, remodeling of rodent neuronal pathways following early lesions can be correlated with spared, beneficial behaviors, as well as maladaptive and detrimental behavior.

Sparing of function following neonatal visual cortex ablation in cats has also been well documented. Cats which sustained such lesions as newborns performed better than animals with later lesions on pattern discriminations (Doty, 1961; Wetzel, et al., 1965; Murphy, et al., 1975), and brightness discrimination (Tucker, et al., 1968). The autoradiographic demonstration of an increased projection from the retina to the pulvinar in cats sustaining visual cortical lesions as neonates (Labar, et al., 1981) has been suggested to contribute to the sparing of visual function in this species. A similar reorganization has been proposed to occur in the rabbit after neonatal visual cortical lesions (Stewart and Riesen, 1972).

The studies of Goldberger and coworkers (Goldberger and Murray,

1974, 1978; Goldberger, 1977, 1981), have implicated plasticity in the recovery of motor function following lesions in the adult animal. Unilateral hindlimb deafferentation by dorsal rhizotomy in the adult cat resulted in the sprouting of ipsilateral descending fibers which were suggested to play a role in the observed recovery of locomotor patterns and some descending reflexes. In animals which sustained partial deafferentation where one dorsal root was spared, the intact root sprouted within the spinal cord and appeared to be responsible for the mediation of recovery. Another study in adult rats (Loesche and Steward, 1977) reported recovery of alteration performance in a T-maze following unilateral entorhinal cortical lesions; this recovery was suggested to be due to the reinnervation of granule cells by sprouting fibers from the entorhinal cortex.

Corticospinal Projection - Origin and Terminations

Found exclusively in mammals, the corticospinal pathway varies in different mammalian orders with respect to trajectory and terminal distribution. In the rat, axons descend from the cortex into the ipsilateral cerebral peduncle, where they occupy the middle two thirds of this large fiber bundle. In the pons, fibers from the peduncle split into bundles surrounded by the basilar pontine nuclei. The corticopontine fibers leave the tract and terminate in the pontine nuclei, while at the lower border of the pons the fibers of the corticospinal tract reunite to form the prominent medullary pyramid, which lies on the ventral surface of the brainstem. The decussation of the pyramidal tract occurs at caudal medullary levels; after crossing in the decussation, a small bundle of fibers known as the Henle-Pick bundle ascends and terminates in the dorsal column nuclei and the spinal trigeminal nucleus, providing the sole source of cortical innervation to these nuclei (Valverde, 1966). The majority of fibers in the pyramidal tract, however, continue caudally to the spinal cord to assume a position which varies among species. In monotremes, insectivores, and elephants the major component of this tract is located within the ventral funiculus, whereas in ungulates, carnivores, lagomorphs, and primates the tract is found in the lateral funiculus. In marsupials, edentates, and rodents the tract is located within the ventral part of the dorsal funiculus. Depending on the species studied, minor components of the tract may be found in any of

the above mentioned positions (Schoen, 1964).

Using the physiological technique of antidromic stimulation, corticospinal fibers were found to give off numerous collaterals during their course to the spinal cord, including fibers to the striatum, the thalamus, the red nucleus, the pontine nuclei, and the reticular formation (Endo, et al., 1973). Furthermore, corticospinal tract fibers that give collaterals to both cervical and lumbar levels have been reported in the spinal cord of cats (Shinoda, et al., 1976; Hayes and Rustioni, 1981) and monkeys (Shinoda, et al., 1979).

As determined by utilizing both anterograde and retrograde tracing techniques on several species, corticospinal fibers originate primarily from the classic motor cortex, Brodmann's area 4 (MI); the premotor cortex, area 6; and from the primary sensory cortex, areas 3,1,2, (SI) (Kuypers, 1958a,b,c, 1960; Nyberg-Hansen and Brodal, 1963; Liu and Chambers, 1964; Jones and Wise, 1977; Wise and Jones, 1977; Hicks and D'Amato, 1977; Murray and Coulter, 1981; Hayes and Rustioni, 1981). Additionally, corticospinal fibers arise from areas 5 of the parietal cortex and the second somatosensory area (SII) in cat (Nyberg-Hansen, 1969), monkey (Murray and Coulter, 1981), and rat (Wise, et al., 1979). The supplementary motor region, previously thought not to make a significant descending spinal projection, has been found to make a major contribution to the corticospinal tract in primates (Catman-Berrevoets and Kuypers, 1976; Murray and Coulter, 1981).

Various studies employing retrograde transport methods to

examine corticospinal projection neurons have reported that layer V is the sole origin of corticospinal fibers in opossum (Ebner, et al., 1976), rat (Hicks and D'Amato, 1977; Wise and Jones, 1977; Ullan and Artieda, 1981), cat (Coulter, et al., 1976), and monkey (Coulter, et al., 1976; Jones and Wise, 1977; Biber, et al., 1978). Labeled cells within primary motor and somatosensory cortex were found arranged in clusters separated by gaps, perhaps reflecting a columnar organization in the sensorimotor cortex (Jones and Wise, 1977; Murray and Coulter, 1981).

Terminations of corticospinal tract fibers have been studied in a variety of species using differing techniques (see Kuypers, 1982, for an extensive review). In the cat, fibers distribute to the nucleus proprius of the dorsal horn and the intermediate gray region, i.e., Rexed's laminae IV-VII (Chambers and Liu, 1957; Nyberg-Hansen and Brodal, 1963), with no terminations in relation to the alpha motoneurons in laminae IX. Accordingly, feline corticospinal fibers activate alpha motoneurons via internuncials (Phillips and Porter, 1977). Studies on the monkey have reported corticospinal terminations within laminae IV-VII as well as directly on motoneurons in the ventral horn (Kuypers, 1958b, 1960; Liu and Chambers, 1964; Kuypers and Brinkman, 1970; Bodian, 1975; Coulter and Jones, 1977). Direct cortico-motoneuronal connections are supported by physiological evidence of monosynaptic transmission to laminae IX (see Phillips and Porter, 1977). Furthermore, the density of direct projections to alpha motoneurons appears to have increased in man (Kuypers, 1958c).

These direct projections are believed to control the fine, independent digital movements characteristic of primates (Kuypers, 1958b). Similar direct corticomotoneuronal projections are also found in the racoon, an animal also capable of discrete digital usage (Petras and Lehman, 1966; Buxton and Goodman, 1967; Wirth, et al., 1974).

Light and electron microscopic studies in the rat have reported that corticospinal fibers terminate in the dorsal horn as well as laminae VII of the intermediate zone (Brown, 1971; Donatelle, 1977). These findings led Brown to conclude that in the rodent the corticospinal tract subserves primarily a sensory function. However, light microscopic Golgi studies (Valverde 1966) demonstrated direct terminations of corticospinal fibers on cervical motoneurons, and a physiological investigation (Elger, 1977), utilizing epicortical stimulation of rat motor cortex, also reported direct cortico-motoneuronal connections at cervical spinal cord levels. Since the rat possesses rather precise digital usage (Castro, 1972), the existence of such direct connections is plausible.

Recent investigations employing retrograde tracing techniques have demonstrated that the corticospinal projection is arranged in a somatotopic pattern in the cat (Coulter, et al., 1976; Groos, et al., 1978), the rat (Wise, et al., 1979), and the monkey (Coulter, et al., 1976; Jones and Wise, 1977; Biber, et al., 1978). These studies indicate that corticospinal axons projecting to lumbosacral levels of the spinal cord arise from neurons located in the hindlimb representation of sensorimotor cortex, those projecting to cervical

levels arise from cells in the forelimb areas of cortex, and those projecting to thoracic levels arise from neurons in intermediate cortical locations.

Corticospinal tract - Function

The corticospinal tract is commonly accepted as the major pathway involved in the control and initiation of skilled purposeful movements, particularly of the hands and fingers (see Brooks and Stoney, 1971 for a review). The pioneering work of Tower (1940) described the effects of unilateral pyramidotomy in monkeys which has since been confirmed by various investigators (Lawrence and Kuypers, 1968; Beck and Chambers, 1970; Laursen, 1971; Woolsey, et al., 1972). The main deficits after pyramidal section as reported by Tower include 1) diminished muscle tone, 2) diminished cutaneous reflexes 3) slow tendon reflexes, and 4) defective initiation and execution of all performance by skeletal musculature, particularly the loss of all discrete usage of digits. Tower summarized pyramidal tract functions in relation to space and time as follows: "The spatial function is the ability to bring into action any portion of the skeletal musculature, in all combinations. This detailed control of the skeletal musculature enables the discrete usage of musculature, especially of the digits, and the modulation of extrapyramidal activity, which are outstanding pyramidal functions. In time, the pyramidal tract operates in two phases. One is a continuous, or tonic, action in effect at all times in the waking state. The other

is a specifically timed increase of discharge, or phasic action, which is evoked in relation to particular situations...together, the tonic function provides for smooth, continuous, efficient action while the phasic function contributes, outstandingly, precision and lability to total performance."

Case studies describing the effects of pyramidal section in man are difficult to evaluate since pathological processes which are confined to the pyramids are quite rare. However, the surgical practice to unilaterally section the cerebral peduncle in patients suffering from hemiballismus, a disease causing extremely violent, involuntary movements, reveals important information. In one such case (Bucy, et al., 1964), the immediate effect of the right peduncular lesion was a flaccid left hemiplegia. After one month the patient demonstrated fairly good use of the left hand, and by seven months he was able to execute fine, individual movements with the left fingers; these movements were only slightly impaired as compared to the right. This degree of recovery is not supported by the results of pyramidal section in monkeys, however, histological examination of the human surgical lesion revealed 17% survival of pyramidal tract axons, which most likely contributed to the recovery of function.

In addition to the effects in humans and other primates, pyramidal tract lesions were found to result in similar deficits in subprimates when appropriately evaluated. Failure of the forelimb digits to grasp tree branches while climbing was observed in the brush-tailed opossum (Hore, et al., 1973). Distal limb movements were

impaired following pyramidal lesions in cats (Gorska and Sybirska, 1980; Dalmeida and Yu, 1981) and dogs (Gorska and Zalewska-Walkowska, 1980), although dogs were less impaired apparently due to their less developed digital dexterity. Pyramidotomy in rats resulted in their inability to grasp small food pellets, which lasted for at least 3 months after surgery (Castro, 1972). Similarly, unilateral pyramidotomy in hamsters (Kalil and Schneider, 1975) resulted in a permanent impairment in manipulatory movements of the contralateral forepaw.

Electrophysiological investigations of motor cortical stimulation following pyramidal tract section largely support the behavioral studies. In the cat, unilateral pyramidal lesion caused an increase in the thresholds of movements elicited from the corresponding hemisphere (Asanuma, et al., 1981). Similarly, pyramidal section in the monkey also resulted in increased thresholds, as well as a lack of independent digital movements following cortical stimulation (Woolsey, et al., 1972). In the dog, the effects of pyramidal section on cortical stimulation were less pronounced than in the cat or monkey (Gorska, et al., 1980), which correlates well with the behavioral data.

Corticopontine Projection - Origin and Terminations

The basilar pontine nuclei provide the most important relay of information from the cerebral cortex to the cerebellum (see Bloedel and Courville, 1981). The morphology of the pontine nuclei has been

studied in detail in a variety of species including the opossum (King, et al., 1968; Mihailoff and King, 1975; Mihailoff, 1978a,b), rabbit and cat (Brodal and Jansen, 1946), rat (Mihailoff, et al., 1981; Mihailoff and McArdle, 1981), monkey (Sunderland, 1940; Nyby and Jansen, 1951; Cooper and Fox, 1976; Cooper and Beal, 1978), and human (Olszewski and Baxter, 1954). Throughout phylogeny the pontine nuclei increase in proportion to the development of the cerebellar hemispheres, and finally reach their peak of development in humans.

Studies using Nissl preparations in several species including the opossum (King, et al., 1968), rabbit and cat (Brodal and Jansen, 1946), and rat (Mihailoff, et al., 1981), have agreed on the presence of four principal pontine nuclei, termed medial, ventral, lateral, and peduncular nuclei in reference to their position in regard to the cerebral peduncle. Also, several smaller subnuclei have been identified in the above studies and include the intrapeduncular, median, dorsomedial, and dorsolateral nuclei. It is agreed that no distinct boundaries or cytological differences serve to separate the various nuclei, and therefore the terminology is primarily useful for descriptive purposes.

Corticopontine projections originate from wide areas of the cerebral cortex (see Sunderland, 1940 and Nyby and Jansen, 1951, for a review of the earlier literature, and also Brodal, 1968a,b, 1971a,b, 1972a,b,c; Mizuno, et al., 1973; Sanides, et al., 1978). The fibers descend via the cerebral peduncle, and terminate primarily in the ipsilateral pontine nuclei, with a slight contralateral projection.

The cells of origin of corticopontine fibers have been investigated utilizing the retrograde HRP technique (Wise and Jones, 1977; Jones and Wise, 1977; Kawamura and Chiba, 1979; Albus, et al., 1981; Wiesendanger and Wiesendanger, 1982a). The majority of labelled cells were found in layer V of somatosensory cortex (SI and SII), motor cortex, and visual cortex, although some cells were found in the cingulate cortex, auditory cortex, and the insular cortex (rostral portion of the rhinal sulcus).

Previous reports had assumed that corticopontine fibers were collaterals from corticospinal neurons (see Allen, et al., 1975), but recent work demonstrates that neurons giving rise to corticospinal fibers appear to be larger and to have a slightly different laminar distribution than corticopontine neurons (Jones and Wise, 1977; Kawamura and Chiba, 1979). Therefore, most of the cortical activation of pontine neurons occurs via direct, separate corticopontine fibers, although some collaterals from corticospinal neurons probably do exist (Endo, 1973; Ruegg, et al., 1977). However, collateral branches of corticopontine axons have been found physiologically to supply the caudate nucleus (Oka and Jinnai, 1978), the superior colliculus and the lateral geniculate body (Albus and Donate-Oliver, 1977).

In most of the species studied, each area of cortex appears to terminate in longitudinal columns throughout particular areas of the pontine nuclei, so that the frontal areas of the cerebral cortex (motor and somatosensory) project to the medial portions of the pontine nuclei, while posterior cortex (visual and auditory) projects

to more lateral portions of the pontine gray (Nyby and Jansen, 1951; Martin and King, 1968; Brodal, 1968; Dhanarajan, et al., 1977; Brodal, 1978; Wiesendanger, et al., 1979; Wiesendanger and Wiesendanger, 1982a). There may be some species differences, however, as indicated by studies in the rabbit (Abdel-Kader, 1968), armadillo (Harting and Martin, 1970), and tree shrew (Shriver and Noback, 1967). Additionally, considerable overlap occurs between projection zones of neighboring cortical areas, and each cortical area terminates in other areas besides its main projection zone. Thus, the corticopontine pathway exhibits both convergence and divergence. Further studies have indicated that the primary sensorimotor cortex in the cat (Brodal, 1968), rat (Mihailoff, et al., 1978), and monkey (Brodal, 1978) projects in a precise, somatotopically organized fashion to the pontine nuclei, with forelimb and hindlimb cortical regions terminating in discrete, longitudinal zones, although with some overlap. In summarizing the characteristics of the corticopontine projection, Brodal (1972) stressed four points: 1) each cortical projection terminates discretely in columns of neurons within the pontine nuclei; 2) each region within the pontine nuclei is impinged on by fibers originating in several regions of the cerebral cortex (convergence); 3) all cortical regions project to more than one pontine region (divergence); and 4) there is a discernible topographical organization in the corticopontine projection, particularly from the sensorimotor cortex.

Although cortical inputs are quantitatively by far the most

important afferent system to the pontine nuclei, several other subcortical areas project to the pontine gray, including the tectum (Kawamura, 1975; Martin, 1969; Burne, et al., 1981), pretectum (Itoh, 1977), ventral lateral geniculate nucleus (Graybiel, 1974), and the deep cerebellar nuclei (Brodal, et al., 1972; Yuen, et al., 1974; Ho and Leong, 1977; McCrea, et al., 1978; Faull, 1978). Additional ascending inputs have also been reported from the dorsal column nuclei (Lund and Webster, 1967; Schroeder and Jane, 1971; Kosinski, et al., 1982), spinal cord (Ruegg, et al., 1978; Swenson, et al., 1982), and the spinal trigeminal nucleus (Swenson, et al., 1982).

Numerous anatomical studies (see Brodal and Jansen, 1946 for a review of the early literature) have revealed that neurons of the pontine gray project predominantly contralaterally to all areas of the cerebellar cortex, with the exception of the nodulus. Projections to the deep cerebellar nuclei, which probably arise from collaterals of axons passing to the cerebellar cortex, have also been described (Kawamura and Hashikawa, 1975). More recent studies utilizing the retrograde HRP technique show that any given zone in the cerebellar cortex receives convergent input from multiple areas of pontine cells (Hoddevik, 1975; Hoddevik, 1977; Brodal and Walberg, 1977; Brodal and Hoddevik, 1978; Brodal, 1979; Mihailoff, et al., 1980; Eisenman, 1980; Eisenman and Noback, 1980; Eisenman, 1981; Mihailoff, et al., 1981; Azizi, et al., 1981). On the other hand, many of these same studies show that certain restricted pontine areas project to multiple cerebellar zones (divergence). The concept of convergence and

divergence within the pontocerebellar system has been confirmed by an anterograde autoradiographic study (Kawamura and Hashikawa, 1981). Since the main afferent input to the pontine nuclei, the corticopontine projection, also displays convergence as well as divergence, the cerebrocerebellar connections are obviously extremely intricate and complex. The consideration that these afferents convey information from motor, somatosensory, visual, auditory, and limbic cortical areas further underscores the complexity of this system.

An Anatomical Investigation of the Topography of Anomalous
Corticopontine and Corticospinal Projections

ABSTRACT

Corticopontine and corticospinal projections from rodent forelimb and hindlimb motor cortex distribute somatotopically within the ipsilateral basilar pontine nuclei and the contralateral side of the spinal cord, respectively. After unilateral sensorimotor cortical lesions in newborn rats, an aberrant increase of crossed corticopontine fibers and an anomalous ipsilateral corticospinal tract are observed originating from the opposite unablated motor cortex. Corticofugal remodelling was not found after cortical lesions in adult animals. By using combined autoradiographic and degeneration staining techniques the increase of crossed corticopontine fibers was found distributed in a topographic pattern similar to the normal ipsilateral corticopontine pattern. Aberrant ipsilateral corticospinal fibers also appeared somatotopic. These anatomical data support the possibility that aberrant motor corticofugal fibers may be functional.

INTRODUCTION

The cerebral cortex exerts a profound influence over cerebellar activity via its extensive input to the basilar pontine gray (Bloedel and Courville, 1981). Various studies have indicated that each area of cortex appears to terminate topographically within the pontine nuclei. For example, motor and somatosensory cortex project primarily to the ventral and medial portions of the ipsilateral pontine gray, while visual and auditory cortex project more laterally in the rat (Wiesendanger and Wiesendanger, 1982), cat (Brodal, 1968), opossum (Martin and King, 1968), and monkey (Dhanarajan, et al., 1977; Brodal, 1978; Wiesendanger, et al., 1979). More specific topographic studies have demonstrated a rather precise somatotopic distribution of forelimb and hindlimb sensorimotor cortical fibers to the ipsilateral basilar pontine nuclei in several species (Brodal, 1968, 1978; Mihailoff, et al., 1978). Similarly, corticospinal fibers terminate somatotopically within the contralateral spinal cord gray as also observed in various species (Coulter, et al., 1976; Jones and Wise, 1977; Biber, et al., 1978; Groos, et al., 1978; Wise, et al., 1979).

In comparison to studies of normal anatomy, analysis of cortical efferent plasticity has revealed the development of anomalous corticofugal projections to the contralateral pontine nuclei (Leong and Lund, 1973; Leong, 1976b; Mihailoff and Castro, 1981; Castro and Mihailoff, 1983) and the ipsilateral spinal cord gray

(Hicks and D'Amato, 1970; Leong and Lund, 1973; Castro, 1975) following cortical ablation in newborn rats. Although aberrant in terms of laterality, these anomalous fibers appear to terminate in areas comparable to their normal projections. However, the precise topography of such anomalous fibers has not been previously examined.

By combining the anterograde tracing techniques of autoradiography and silver degeneration staining, this study was undertaken to examine more precisely the distribution of aberrant fore- and hindlimb motor cortical efferent fibers. The observed somatotopy of aberrant pathways as found in the present investigation is thought to provide an anatomical basis for the possible functional significance of corticofugal plasticity.

A preliminary account of part of this study has previously appeared in abstract form (Kartje-Tillotson, et al., 1981).

MATERIALS AND METHODS

Subjects

Long-Evans, black hooded rats were divided into two experimental groups receiving neonatal right SMC lesions (n=9) or similar unilateral SMC lesions as adults (n=4). At 3-5 months postoperative, projections from the opposite unablated SMC were mapped in comparison to normal adult controls (n=13).

Surgical Procedures

Using 2-day old pups anesthetized by hypothermia, the cranium was exposed with a midline skin incision and the skull overlying the right frontal and parietal cortex was removed with forceps. The dura was opened and the right SMC region was removed by aspiration with a small pipette. The wound was packed with gelfoam and the skin sutured together. The pups were warmed under an incandescent lamp, returned to their mothers until weaning, and then housed individually until used in the cortical mapping study at 3-5 months of age.

In the adult experimental group, large SMC lesions were made in previously unoperated three month old rats using sodium pentobarbital anesthesia (40mg/kg delivered intraperitoneally) followed by 0.05 mg of atropine sulfate. After securing the animal in a stereotaxic headholder, the skull was exposed with a midline skin incision, and the bone over either the right or left frontal cortex was removed with rongeurs. The dura was opened and the SMC region was removed by

aspiration. The wound was packed with gelfoam, the skin sutured together, and the animals were returned to their cages. Four to five months later, animals were prepared for cortical micromapping procedures as described below.

Movements evoked by intracortical microstimulation were mapped in order to identify the fore- and hindlimb motor cortical areas in the opposite unablated hemisphere in both experimental groups and in non-lesion controls. Animals were anesthetized with ketamine hydrochloride (100 mg/Kg delivered intraperitoneally followed by 0.05 mg of atropine sulfate). Supplemental doses of 20 mg/kg of ketamine were given as needed to prevent spontaneous movements. Animals were secured in a stereotaxic headholder with their body resting on a heating pad in order to maintain rectal temperature at 36-38 degrees C. The hair on both the forelimbs and hindlimbs was clipped, and the limbs were allowed to hang free to better facilitate observation of movements. The cisterna magna was opened and drained to reduce swelling of the cortex, and the left cortical surface was exposed and covered with warm mineral oil. The dura was left intact since it was initially found that removal of the dura caused subsequent cavitation in the cortex which would likely confuse the results obtained from degeneration staining.

A sharpened, glass-insulated, tungsten wire with a 100 micron tip served as the stimulating electrode. Using bregma as a reference point and utilizing the maps of Hall and Lindholm (1974) and Neafsey and Sievert (1982), the fore- and hindlimb motor areas were explored

in 0.5 mm steps in both a medio-lateral and rostro-caudal direction in order to determine their exact boundaries. Stimulation currents (5-100 uamps) were applied with a frequency of 350 hz in 300 msec trains and 0.25 msec pulses, at a depth of 1.7 mm and were monitored on an oscilloscope by measuring the voltage drop across a 10,000 ohm resistor. For each stimulation point the type of movement elicited as well as the stimulus current threshold, i.e., the minimum current that would elicit a movement, was recorded.

Identification of fore- and hindlimb motor cortex facilitated the localized placement of various combinations of lesions and injections of tritiated leucine. In the neonatal lesion group and in several controls, lesions of forelimb and injections of hindlimb areas (or vice versa) were combined in individual animals. Small lesions approximately 1-2mm in size were made by aspiration with pipettes (approximately 0.5 to 1.0mm in diameter). Tritiated leucine (specific activity 152.0 Ci/mole, in 0.01 N hydrochloric acid with a final concentration of 50 uCi/ul) was injected using a 1 ul Hamilton microsyringe fitted with a glass tip having a 30-50 micron diameter. A total volume of 0.2-0.3 uliters (1-2 injection sites per animal) was slowly injected over a 20 minute time interval. In the adult lesion group, a volume of 0.4-0.8 ul of tritiated leucine was spread over four injection sites throughout the spared SMC, and two control animals were similarly treated.

Histological Methods

At 7-10 days after placement of precise lesions and/or injections, animals were overdosed with sodium pentobarbital and perfused through the heart with saline followed by 10% buffered formalin. Brains and spinal cords were removed, photographed, and placed in a 30% sucrose and 10% formalin solution until they sank. Transverse sections (35 microns) were cut on a freezing microtome into a 2% buffered formalin solution. Sections from animals sustaining forelimb or hindlimb cortical lesions were processed by the Fink-Heimer (1967) method for degenerating axons, and those from animals receiving tritiated leucine injections were processed for autoradiography. Alternate sections from the combined lesion-injection animals were processed according to both procedures. According to the autoradiographic protocol of Chan-Palay (1977), sections were mounted on subbed slides and defatted in xylene. Slides were then dipped in a 1:1 mixture of Kodak NTB-2 emulsion and distilled water at 42 degrees C. in a humidified darkroom. Slides were allowed to dry in a rack and placed in light-tight dehumidified boxes for 4-8 week exposures at 4 degrees C. After the appropriate exposure time, slides were developed for four minutes in full strength D19 developer at 14-16 degrees C., rinsed in tap water for 30 seconds, and fixed in Kodak rapid fixer for five minutes. Slides were then washed for 45 minutes in running tap water and subsequently stained with cresyl violet and coverslipped. Slides of both control and experimental animals were always processed simultaneously to rule out differences in labeling due to changes in temperature, humidity, etc.

Autoradiographs were examined using darkfield microscopy.

The distribution of degenerating and tritium labelled fibers was plotted using a camera lucida microscope attachment. The principal subdivisions of the rodent pontine gray are illustrated in figure 1 which is derived from studies reported by Mihailoff, et al (1981) which showed that the rodent pontine gray is similar to that of other species. Since the pontine gray cannot be separated on the basis of cytological differences, subdivisions are named relative to their position to the cerebral peduncle.

RESULTS

Normal Corticopontine Topography

The projection pattern of degenerating fibers to the basilar pontine nuclei as observed after placement of small lesions in forelimb motor cortex in normal animals (Fig. 2a) is illustrated in Fig. 3. Degenerating fibers traversed the medial two-thirds of the ipsilateral cerebral peduncle, sparing its most medial aspect, and distributed in five discrete columns running longitudinally through the ipsilateral pontine gray. The most dense degeneration was found at rostral levels within the ventropeduncular and ventral nucleus (Fig. 3, levels A-B, Fig. 4A). Moderate amounts of degeneration were found ventromedially within the medial nucleus at mid pontine levels (Fig. 3, levels D-E, Fig. 4B). A third area of degeneration was located ventrally within the ventral nucleus just above fibers of the middle cerebellar peduncle, becoming more extensive mid caudally (Fig. 3, levels C-E, Fig. 4C). A fourth ventrolateral zone, located on the border between the ventral and lateral pontine nuclei, was only lightly filled with degeneration (Fig. 3, level E, bold arrow). A fifth zone was observed dorsal to the cerebral peduncle in the dorsal peduncular nucleus (Fig. 3, C-E, Fig. 4D). A paucity of forelimb terminations were found at caudal levels of the pontine gray (Fig. 3, F-G). Additionally, light degeneration was located in the medial Pontine nucleus contralateral to the forelimb lesion (Fig. 3, D-E,

small arrows).

The projection pattern of labeled fibers to the pontine nuclei as observed after placement of small injections of tritiated leucine in hindlimb motor cortex in normal animals (Fig.2b) is illustrated in Fig. 5. Labeled fibers were primarily restricted to the lateral two-thirds of the ipsilateral cerebral peduncle. Similar to the forelimb projection, label was found in five ipsilateral longitudinal columns, however, the densest projection was to caudal pontine levels. A discrete zone of label was found in the dorsal aspect of the ventral nucleus at rostral pontine levels (Fig.5, levels A-B, Fig.6A). Labeled terminals were also found in a second area within the medial pontine nucleus extending from mid to caudal pons (Fig.5, levels D-G). A third zone of label was located on the ventral border within the ventral nucleus. Labeling within this zone was light at mid pontine levels (Fig.5, levels D-E, Fig.6C), but increased in density at caudal levels (Fig.5, levels F-G, Fig.6D). In fact, at caudal levels the label was so dense that discrete columns of termination could not be discerned and instead the ventral zone appeared to merge with the medial column into one continuous band (Fig.5, levels F-G, Fig. 6D). A fourth ventrolateral area of label also appeared to merge with the ventral column of terminations (Fig.5, level F). A fifth zone of label was located in the dorsal peduncular nucleus at mid pontine levels (Fig.5, levels C-D, Fig.6B). Furthermore, a slight contralateral projection was apparent at caudal pontine levels in the ventral nucleus (Fig.5, level F, small arrows).

In order to demonstrate the topographic relationships of forelimb and hindlimb motor cortical projections, the results after cortical forelimb lesion and hindlimb injection of tritiated leucine in the same animal are presented in Fig.7. The forelimb (fine dots) and hindlimb (large dots) projections appear to have differential sites of termination, with forelimb more rostral and hindlimb more caudal. However, some overlap does occur, such as in the ventral nucleus at rostral levels (Fig.7, A-B), the dorsal peduncular nucleus (Fig.7, C-D), and the medial pontine nucleus (Fig.7, D-E).

Topography of Sprouted Corticopontine Fibers

Selective ablation of forelimb motor cortex was combined with injection of hindlimb motor cortex in adult animals that sustained large sensorimotor cortical lesions of the opposite hemisphere at 2 days of age. Analysis of alternate sections stained for degenerating fibers or processed autoradiographically revealed a somatotopic distribution of the aberrant, crossed corticopontine fibers (Fig.8). Degeneration from the small forelimb cortical lesion was observed to cross the midline at mid-pontine levels and terminate contralaterally in the medial and ventral pontine nuclei (Fig.8, D-E, Fig.9A). Labeled fibers from the hindlimb cortical injection decussated more caudally and distributed to the contralateral medial and ventral nuclei (Fig.8, F-G, Fig.9C). Sprouted fibers did not appear to segregate into discrete columns as was found in the normal ipsilateral projection. Instead, anomalous fibers tended to cross the midline and

course along the ventral surface of the contralateral pontine gray. The distribution of cortical forelimb and hindlimb fibers to the ipsilateral pontine nuclei appeared normal.

Corticopontine Topography Following Adult SMC Lesion

Autoradiographic analysis of corticopontine projections in animals that sustained SMC ablations at maturity revealed a normal distribution pattern in the pontine gray. As in normal control animals, cortical fibers terminated in continuous rostro-caudal columns throughout the ipsilateral pontine gray, while at low pontine levels the columns merged into one continuous band (Fig.9D). Similar to controls, light label was found in the medial and ventral pontine nuclei in the contralateral pontine gray. Therefore, no apparent increase in the crossed corticopontine projection was detected (compare Fig.9D with Fig.9C).

Corticospinal Topography

Selective placement of forelimb motor cortical lesions in control animals demonstrated degenerating fibers coursing through the base of the dorsal funiculus on the contralateral side of the cervical spinal cord. Degeneration argyrophilia was primarily confined to the dorsal horn (excluding the substantia gelatinosa and the marginal nucleus) and the central part of the intermediate gray (Fig.10a). Only scarce degeneration could be detected at lumbar levels (Fig.10b).

In animals sustaining neonatal SMC ablations, selective placement of forelimb motor cortical lesions in the spared hemisphere revealed anomalous fibers coursing through the base of the ipsilateral dorsal funiculus in addition to the more dense contralateral corticospinal tract. These anomalous fibers terminated in the ipsilateral gray matter at cervical levels only (Fig.11a, Fig.12a), with no apparent terminations at lumbar levels. Although less dense than the normal contralateral projection, the aberrant fibers distributed to comparable areas in the ipsilateral gray matter.

DISCUSSION

Normal Corticopontine Topography

The results from this study support earlier investigations in the rat (Mihailoff, et al., 1978; Wiesendanger and Wiesendanger, 1982), cat (Brodal, 1968), and monkey (Brodal, 1978), which describe a somatotopic projection from the sensorimotor cortex to the basilar pontine nuclei. Similar to autoradiographic studies in the rat (Mihailoff, et al., 1978; Wiesendanger and Wiesendanger, 1982), fibers from forelimb and hindlimb motor cortex terminated in five discrete longitudinal columns in the ipsilateral pontine nuclei. Axons originating from forelimb cortical areas distributed rostrally in these longitudinal columns in contrast to fibers from hindlimb motor cortex which terminated at more caudal levels, although some overlap did occur.

A small contralateral projection from motor cortex to the pontine nuclei was also found to distribute somatotopically. The existence of a normal contralateral corticopontine projection is in agreement with previous reports in the rat (Mihailoff, et al., 1978; Wiesendanger and Wiesendanger, 1982; Castro and Mihailoff, 1983), opossum (Martin and King, 1968), and phalanger (Martin, et al., 1971). However, normal contralateral corticopontine fibers were not found in cats (Brodal, 1968) or primates (Dhanarajan, et al., 1977, Brodal, 1978).

Topography of Sprouted Corticopontine and Corticospinal Fibers

The observed increase of crossed corticopontine fibers after unilateral SMC lesion in newborn rats is in agreement with previous light (Leong and Lund, 1973; Castro and Mihailoff, 1983) and electron microscopic studies (Mihailoff and Castro, 1981). Significantly, findings from the present study indicate that aberrant corticopontine fibers distribute to the contralateral pontine gray in a somatotopic manner. Anomalous fibers originating from forelimb motor cortex terminated in medial and ventral pontine nuclei at rostral levels of the pontine gray, while sprouted fibers from hindlimb cortex distributed to these same nuclei although at more caudal levels.

Other studies of corticopontine plasticity have demonstrated an apparent specificity in that no alteration in the distribution of sensorimotor-pontine fibers was observed after neonatal occipital cortical lesions, nor was remodelling found in the reverse lesion sequence, i.e., no apparent remodelling of occipito-pontine fibers was found after neonatal SMC lesions (Castro and Mihailoff, 1983).

The topographic distribution of anomalous fibers has also been shown in the visual system, including anomalous retinofugal axons (Cunningham and Speas, 1975; Frost and Schneider, 1976, 1979; Finlay, et al., 1979; Lent and Mendez-Otero, 1980), and corticotectal axons (Mustari and Lund, 1976; Rhoades and Chalupa, 1978). Although not extensively studied, other investigators have noted the ordered, topographic distribution of anomalous corticostriate (Goldman, 1978)

and corticorubral (Nah and Leong, 1976a) fibers.

In the present study, the distribution of aberrant crossed fibers coincided with the distribution of normal contralateral fibers, i.e., sprouting occurred at pontine levels which normally received a contralateral projection. This suggests that the observed remodelling of pontine inputs may reflect an increased collateralization of normally crossed fibers. In support of this idea, an electrophysiological study of anomalous cerebello-thalamic fibers (Yamamoto, et al., 1981) found that 22% of the aberrant fibers were collaterals from the normal projection. However, it is also likely that anomalous corticopontine axons may represent re-directed fibers which were originally destined for the ipsilateral pontine gray. A recent study utilizing retrograde double labeling techniques (Gramsbergen and Ijkema-Paassen, 1982) concluded that aberrant cerebello-rubral fibers were derived from separate parent cells and were not collaterals from normally projecting fibers. In the corticopontine system, the possibility exists that both collateralization of normal contralateral axons as well as the re-direction of ipsilateral fibers may occur. This question could be resolved by the application of double retrograde labeling techniques (Bentivoglio, et al., 1980).

Although aberrant crossed corticopontine fibers distributed to areas deprived of inputs by the neonatal lesion, not all such areas received anomalous cortical inputs. For example, the dorsal peduncular nucleus and mid to rostral levels of the ventral nucleus

did not receive anomalous crossed corticopontine inputs. The lack of normal crossed inputs to these areas, in comparison to the small, normal input to regions demonstrating sprouting, may reflect a sprouting mechanism which is dependent upon a certain number of normally present fibers. It is also possible that pontine afferent fibers from other cortical areas (see Wiesendanger and Wiesendanger, 1982) may have sprouted into these zones and thereby precluded the remodelling of forelimb and hindlimb motor cortical afferents. Additionally, other pontine afferent systems, such as inputs from the tectum (Burne, et al., 1981), dorsal column nuclei (Kosinski, et al., 1982), or the spinal cord (Ruegg, et al., 1978; Swenson, et al., 1982), may have expanded their terminal fields to synapse in these deafferented areas and thus prevent corticopontine remodelling. The notion that one afferent system may influence the distribution of other afferent systems has previously been proposed as the "critical afferent theory" as derived from studies of hippocampal plasticity (Cotman, et al., 1981).

The development of an aberrant ipsilateral corticospinal tract after unilateral SMC lesion in newborn rats is in agreement with earlier studies (Hicks and D'Amato, 1970; Leong and Lund, 1973; Castro, 1975). Previous investigations at the ultrastructural level have indicated that this aberrant tract makes structurally normal synaptic contacts in the spinal gray matter (McClung and Castro, 1975; Leong, 1976a). Results from the present study demonstrate that anomalous fibers originating from forelimb motor cortex terminate

topographically in cervical levels of the spinal cord, primarily in the region of the dorsal horn. No aberrant fibers were apparent at lumbar spinal cord levels. These findings provide the anatomical basis for the electrophysiological studies described in the next section.

The orderly, somatotopic distribution of anomalous corticopontine and corticospinal fibers suggests that mechanisms governing sprouting are similar to those regulating normal developmental axonal-target interactions. A recent developmental study in the rat demonstrates that the corticopontine projections are present at birth (Schreyer and Jones, 1982), indicating that the neonatal cortical lesions employed in the present study had disrupted existent cortico-efferent pathways and consequently deafferented the pontine gray. Therefore, the observed increase in crossed projections from the spared SMC may represent a reinnervation of pre-existing postsynaptic sites. The reoccupation of such sites by anomalous fibers could provide a relatively simple mechanism for the establishment of an orderly, topographic distribution. The theory that terminal space availability induces sprouting of neuronal pathways was first proposed by Schneider (1970, 1973) in regard to visual system remodelling.

Although light microscopy reveals that cortico-efferent fibers have reached the level of the pontine gray in the newborn rat, Golgi studies suggest that synaptogenesis in the pontine nuclei is delayed until postnatal day 12, since pontine neurons at this time demonstrate

a dramatic increase in dendritic complexity (Adams, et al., 1980). Accordingly, electron microscopic analysis demonstrates few axonal boutons in the pontine neuropil until postnatal day 5 (Mihailoff, 1982). The possibility of a normal delay in synapse formation suggests an alternative hypothesis that the observed corticopontine remodelling may reflect an actual increase in growth and synaptic potential in the developing corticopontine pathway.

Developmental studies in the rat (Donatelle, 1977; Schreyer and Jones, 1982) indicate that corticospinal fibers have reached cervical spinal cord levels at birth, although terminations in the cervical gray matter are not apparent until postnatal day 5. The effect of the neonatal cortical lesions employed in the present investigation was to prevent the development of corticospinal terminations rather than to remove them. Consequently, growth of the anomalous ipsilateral corticospinal tract was into areas previously devoid of afferent inputs. Therefore, the somatotopic distribution of this aberrant tract cannot be simply explained by the take over of pre-existing post synaptic space. However, it should be noted that presynaptic growth cones, which may be present in the spinal cord neuropil at the time of neonatal lesion, have been shown to influence the development and maintenance of neurons in the chick embryo (Peusner and Morest, 1977).

Functional Implications

The aberrant growth of corticopontine and corticospinal fibers to appropriate terminal zones suggests that these anomalous

projections are correctly "rewiring" parts of the CNS which were previously disrupted due to neonatal cortical damage. The ability of new connections to form in an ordered, precise manner, as opposed to a random, non-specific fashion, is important from a functional point of view. Although the functional role of neuronal plasticity is not completely understood (Johnson and Almlil, 1978; Schneider, 1979; Gramsbergen, 1981), several studies have correlated anomalous pathways with sparing of function (Hicks and D'Amato, 1970; Goldberger and Murray, 1974, 1978; Devor, 1975; Loesche and Steward, 1977; Labar, et al., 1981). Recent electrophysiological evidence from our laboratory indicates that anomalous cortico-efferent pathways are capable of influencing ipsilateral forelimb movements (Kartje-Tillotson, et al., 1982). Additionally, a recent investigation utilizing 2-deoxyglucose as a marker for metabolic activity reported bilateral activation of the basilar pontine nuclei after unilateral stimulation of the spared motor cortex in rats sustaining neonatal cortical lesion (Sharp and Evans, 1983). These findings indicate that the aberrant crossed corticopontine projection is metabolically active and therefore functional.

Corticopontine Topography Following Adult SMC Lesion

Although CNS remodelling has been documented following lesions in the adult animal (Liu and Chambers, 1958; Raisman, 1969; Cotman and Lynch, 1976; Goldberger, 1977, 1981; Tsukahara, 1981; and see Cotman, et al., 1981 for a review), not all CNS pathways retain the ability to

form new connections beyond the perinatal period (Schneider, 1970, 1973; Devor, 1976; Nah and Leong, 1976a; Frost and Schneider, 1979; Nah, et al., 1980). Of particular relevance to this investigation are studies of the rat which have shown that aberrant ipsilateral corticospinal fibers will develop in response to unilateral cortical lesions in animals up to 17 days of age, but not after lesions in older animals (Hicks and D'Amato, 1975; Leong, 1976b). Similarly, the present study indicates that corticopontine sprouting does not occur following adult cortical ablations. Considering the large and therefore adequate size of the adult lesions used in this study, the successful transport of label based on the density of ipsilateral fibers, and the 5-6 month interval between lesion and injection, the observed lack of corticopontine sprouting after adult cortical lesions appears well established. However, the question concerning adult corticopontine sprouting is still unresolved since Mihailoff has observed such sprouting in rats subjected to adult SMC lesions (personal communication).

In conclusion, our results indicate that anomalous fibers in the corticopontine and corticospinal systems terminate somatotopically into functionally appropriate pontine and spinal cord areas. The orderly distribution of sprouted pathways suggests that these anomalous fibers are regulated by the same factors which guide growing axons in normal development. Furthermore, the ability of the CNS to anatomically remodel in an orderly manner indicates that plasticity

may play a role in recovery of function following brain damage in the young animal.

Fig. 1. Diagrammatic illustration of the principle nuclei of the basilar pontine gray as modified from Mihailoff, et al., 1981.

dPd=dorsal peduncular nucleus; vPd=ventral peduncular nucleus;
dL=dorsolateral nucleus; Med=medial nucleus; Lat=lateral nucleus;
Vent=ventral nucleus; mcp=middle cerebellar peduncle;
ped=cerebral peduncle.

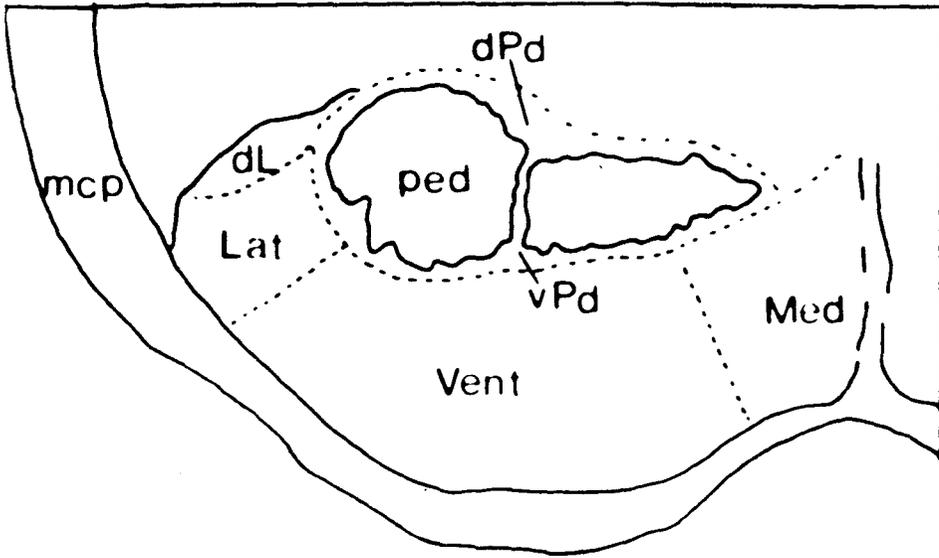


Fig. 2. Representative coronal sections through adult cortical forelimb lesions/hindlimb injections for normal animals (A and B) and animals sustaining neonatal cortical lesion (C and D).

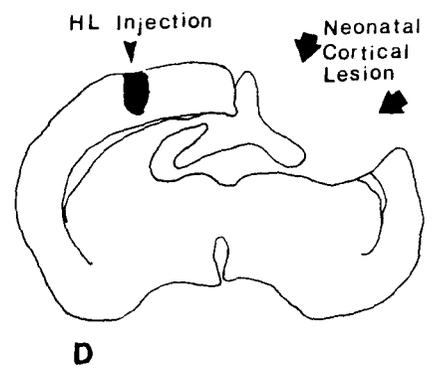
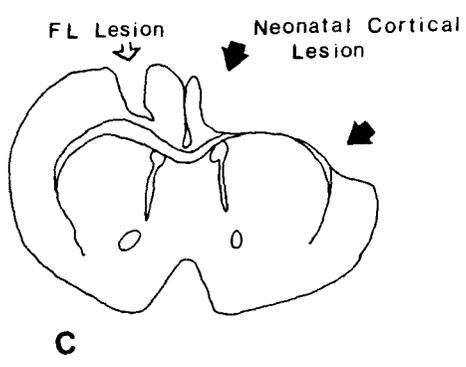
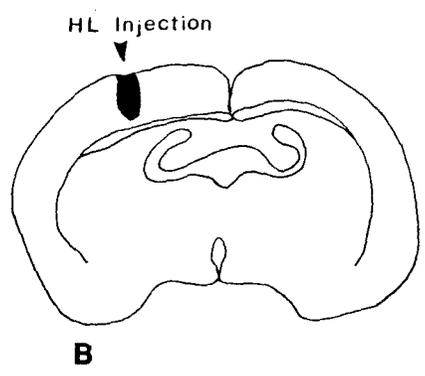
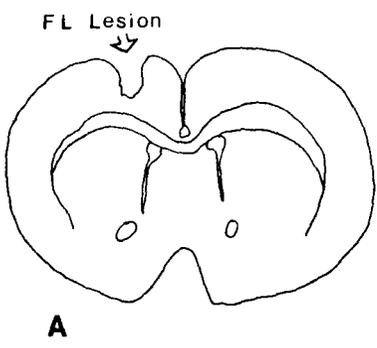


Fig. 3. A sequence of camera lucida drawings through the rostral to caudal (A-G) extent of the pontine gray demonstrating the distribution of degenerating axons observed using the Fink-Heimer stain after an adult forelimb motor cortical lesion in a control animal as illustrated by the drawing in the upper left corner. For this figure and all subsequent camera lucida drawings through the PG, individual levels are spaced at 280-300 microns, and the nuclear divisions indicated in level D correspond to Fig. 1. Boxes labeled A-D correspond to photomicrographs in Fig.4 and indicate four separate areas of termination. The bold arrow (level E) indicates a fifth zone of termination. The small arrows on the right side of the PG (levels D-E) indicate contralateral terminations. FL=forelimb; ped=cerebral peduncle; pg=pontine gray; mcp=middle cerebellar peduncle.

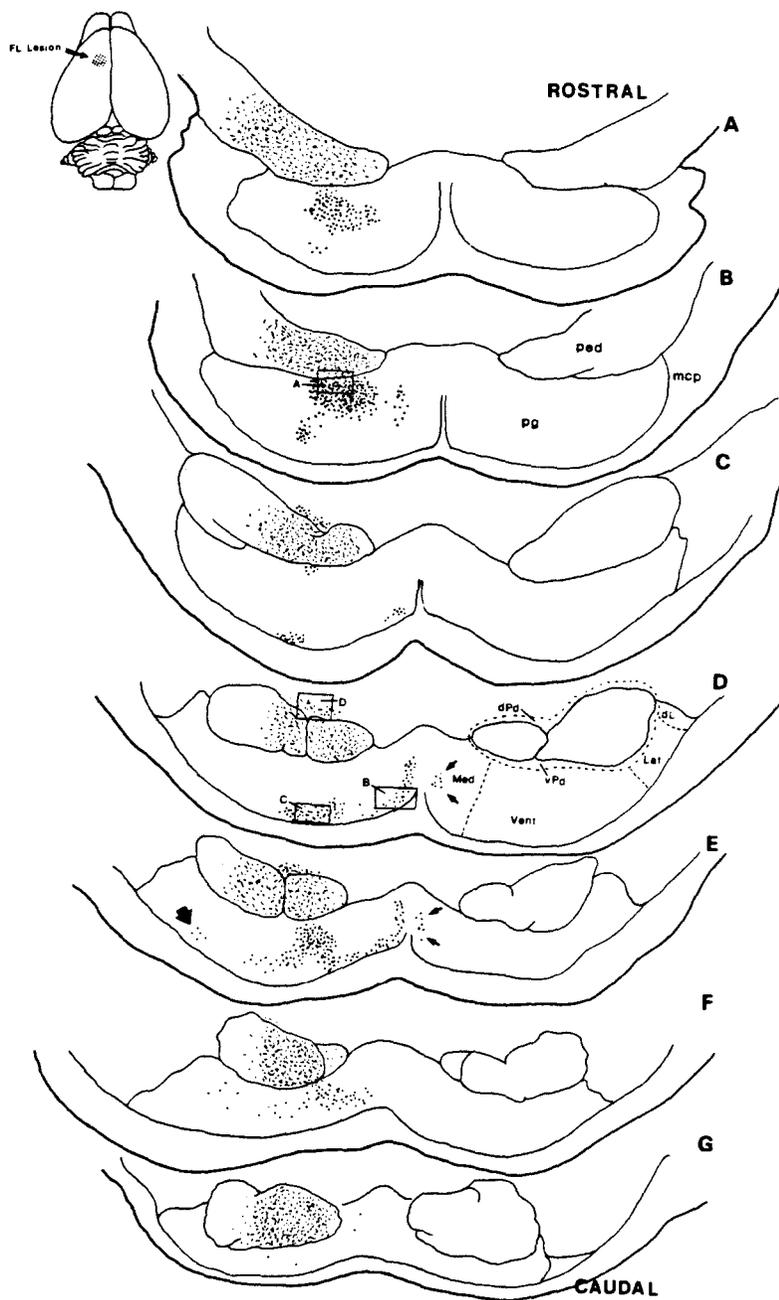


Fig. 4. Photomicrographs corresponding to boxes labeled A-D in Fig. 3. Fink-Heimer stain. 120x. A. Ventral peduncular and ventral pontine nuclei. B. Medial pontine nucleus. C. Extreme ventral portion of the ventral pontine nucleus. D. Dorsal peduncular nucleus.

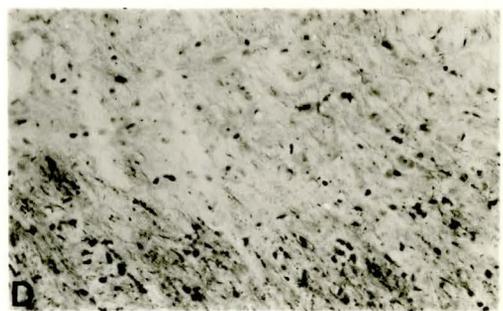
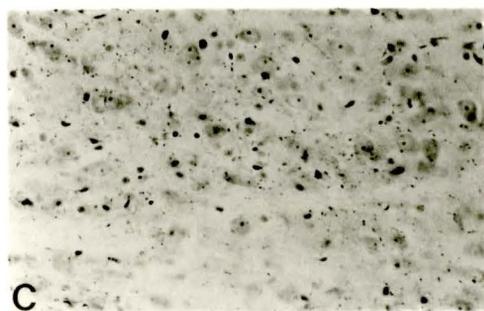
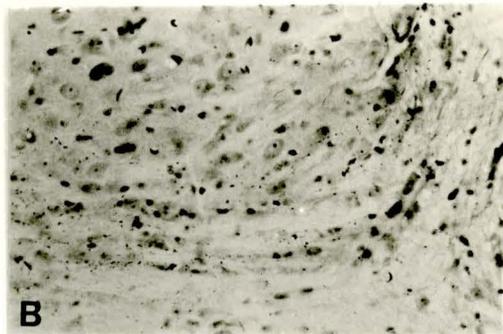


Fig. 5. A sequence of camera lucida drawings demonstrating the distribution of labeled axons in the PG after an adult motor cortical hindlimb injection of tritiated leucine in a normal animal as illustrated by the drawing in the upper left corner. Small arrows (level F) indicate the small contralateral projection. HL=hindlimb; ped=cerebral peduncle; pg=pontine gray; mcp=middle cerebellar peduncle.

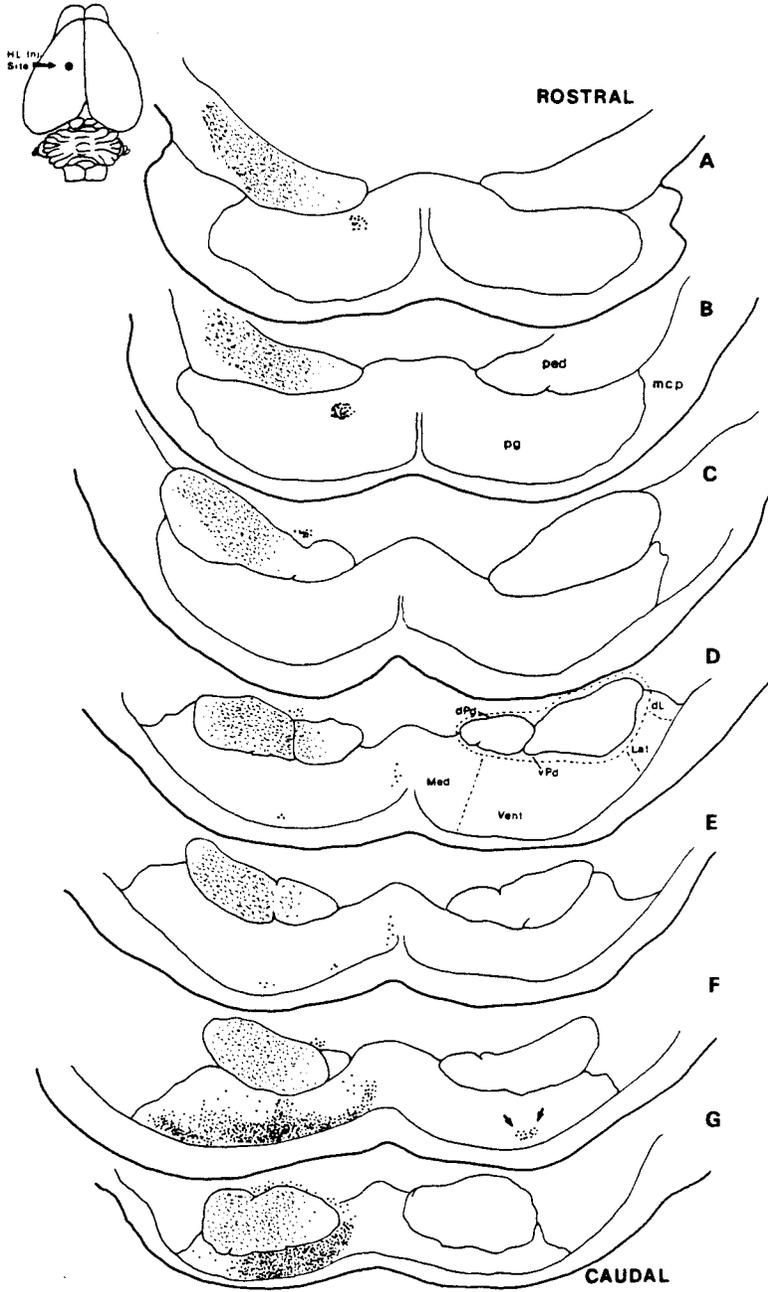


Fig. 6. Low power photomicrographs from a control animal demonstrating the distribution of labeled terminal fibers following an adult motor cortical hindlimb injection of tritiated leucine. Darkfield. 30x. A. Terminal labeling in the ventral pontine nucleus at rostral levels (corresponding to Fig.5, level B). B. Labeling in the dorsal peduncular nucleus (corresponding to Fig.5, level C). C. Light label in the extreme ventral zone of the ventral nucleus at mid pontine levels (Corresponding to Fig.5, level E). D. Dense label at caudal pontine levels (corresponding to Fig.5, level G).

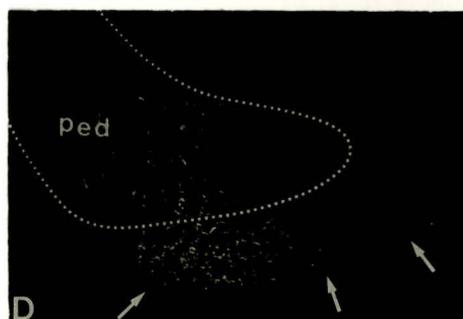
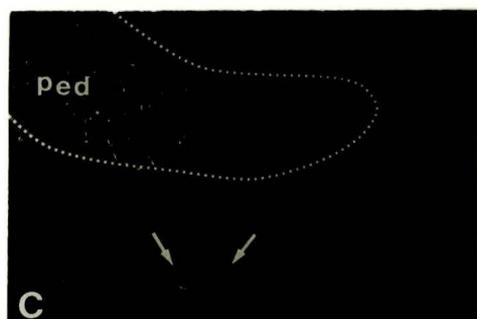
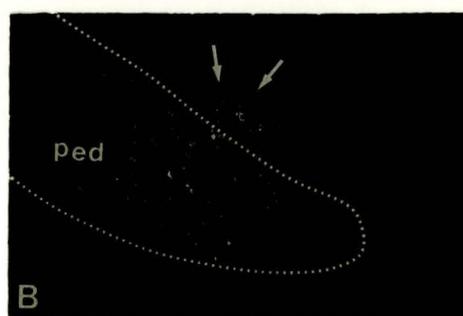
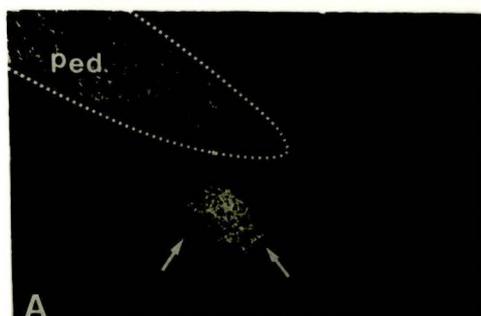


Fig. 7. A sequence of camera lucida drawings demonstrating the combined distribution of fibers from forelimb motor cortex (small dots) and hindlimb motor cortex (large dots) in a control animal. The drawing in the upper left corner indicates the area of the small cortical forelimb lesion and the cortical hindlimb injection of tritiated leucine. FL=forelimb; HL=hindlimb; ped=cerebral peduncle; pg=pontine gray; mcp=middle cerebellar peduncle.

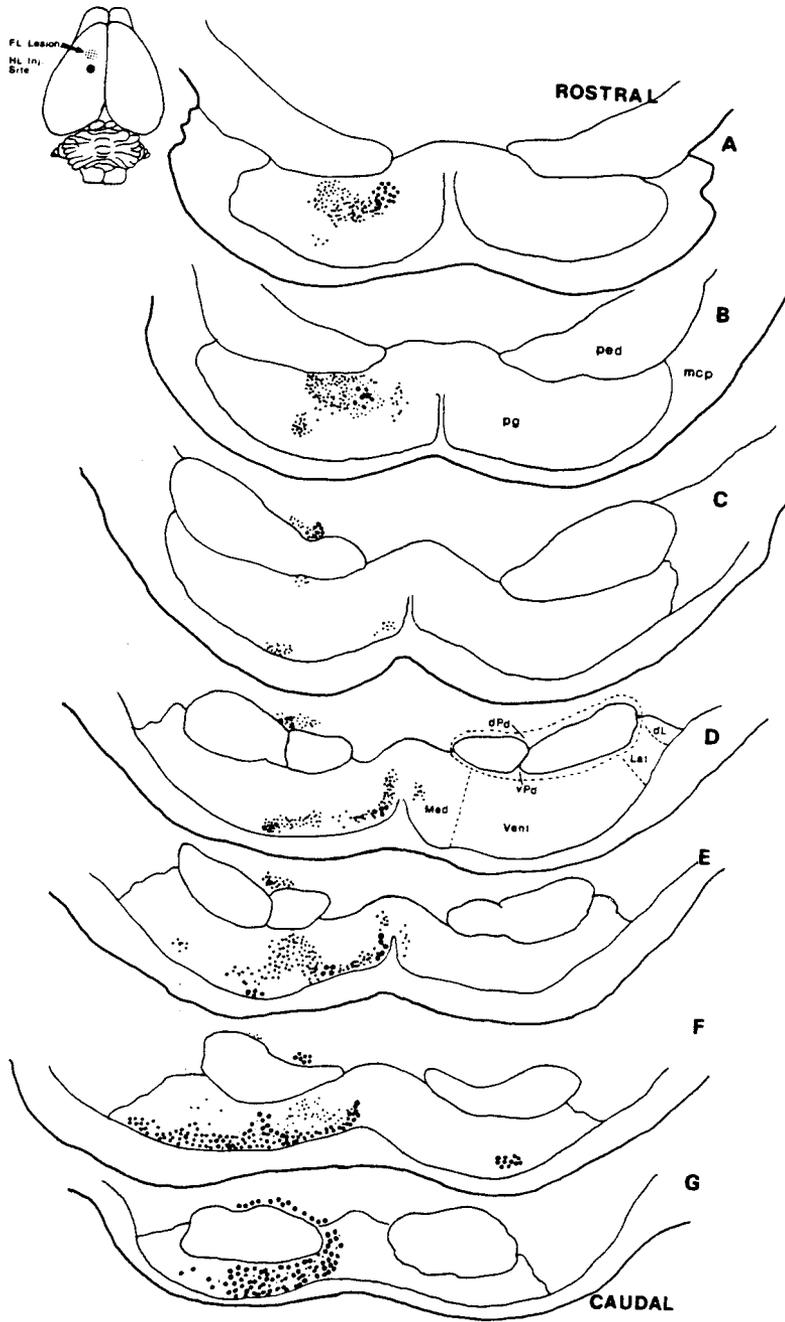


Fig. 8. A sequence of camera lucida drawings demonstrating the combined distribution of fibers from forelimb motor cortex (small dots) and hindlimb motor cortex (large dots) in an animal which sustained a neonatal SMC lesion. Boxes labeled A (level D) and B(level G) correspond to photomicrographs in Fig.9. Same abbreviations as in Fig.7.

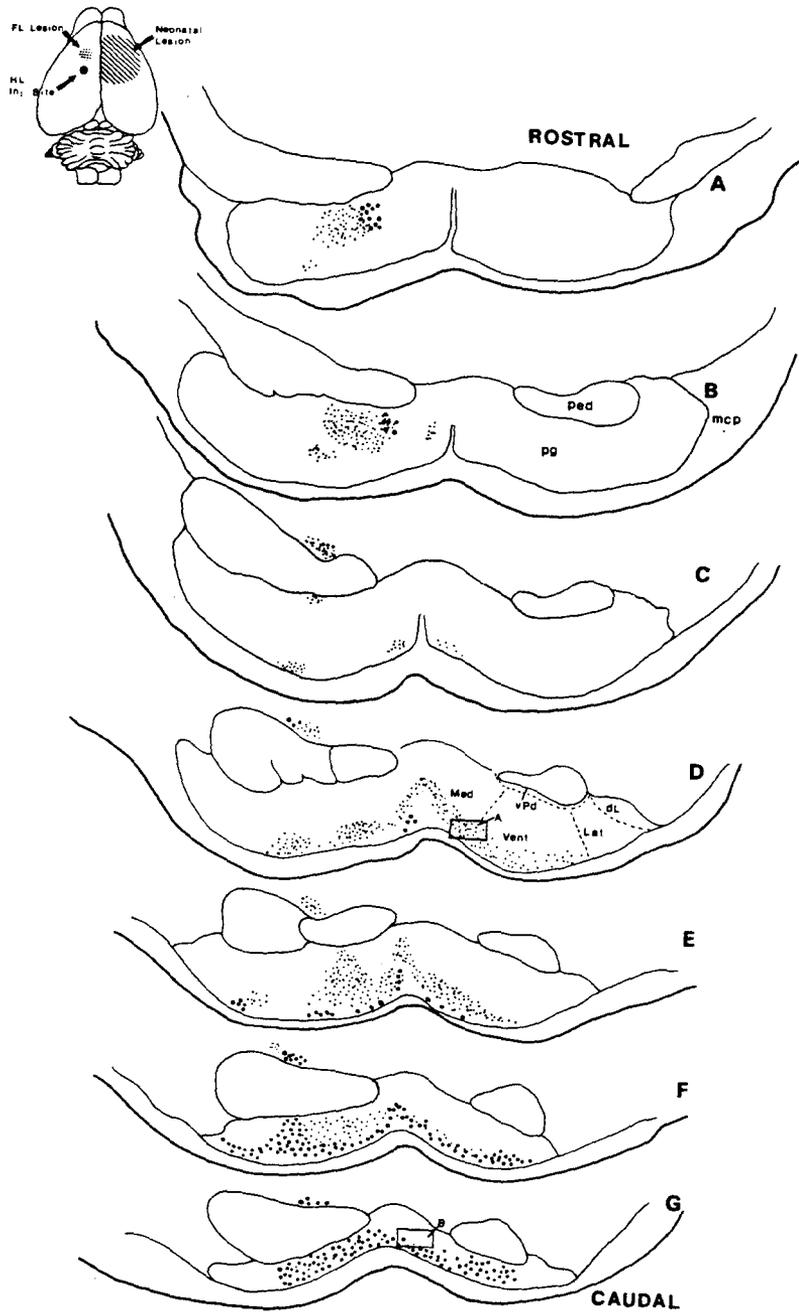


Fig. 9. A and B. Photomicrographs corresponding to the boxes labeled A and B in Fig.8. Fink-Heimer stain. 120x. A. Dense degeneration from the adult cortical forelimb lesion in the contralateral PG at mid pontine levels. B. Apparent lack of degenerating fibers to caudal levels of the PG. C. Photomicrographs demonstrating the increase in terminal labeling to the contralateral PG after tritiated leucine injection into the spared hindlimb motor cortex of an animal sustaining neonatal SMC lesion (corresponding to Fig.8, level G). Bold arrow indicates the midline. Darkfield. 30x. D. Photomicrograph demonstrating terminal labeling in the ipsilateral PG after tritiated leucine injection into the spared motor cortex of an animal sustaining an adult SMC lesion. Note the apparent lack of sprouting over the midline as indicated by the bold arrow. Darkfield. 30x.

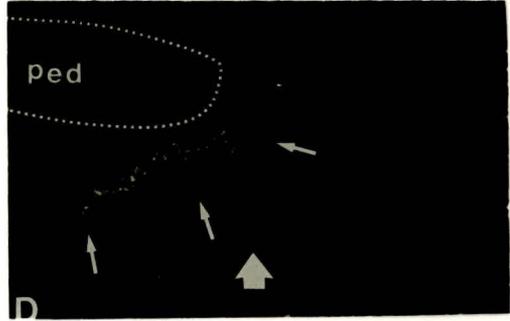
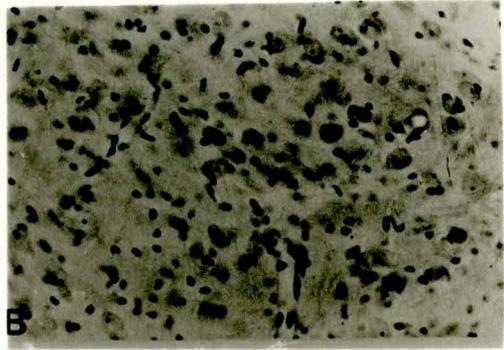
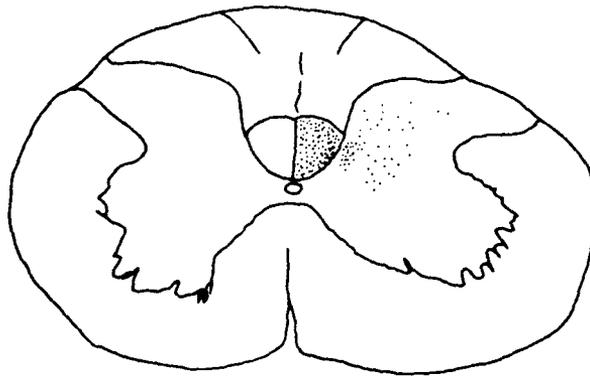
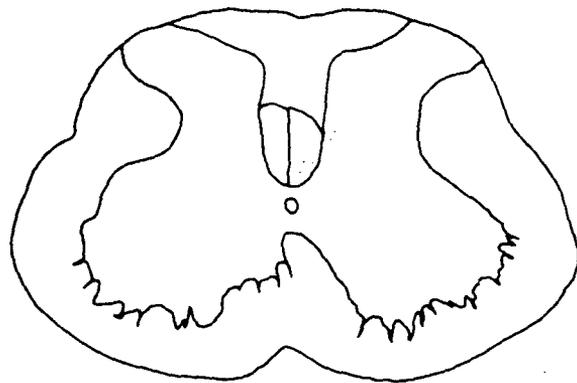


Fig. 10. Camera lucida drawings through cervical (A) and lumbar (B) levels of the spinal cord demonstrating the distribution of degenerating axons observed using the Fink-Heimer stain after an adult forelimb motor cortical lesion in a control animal.

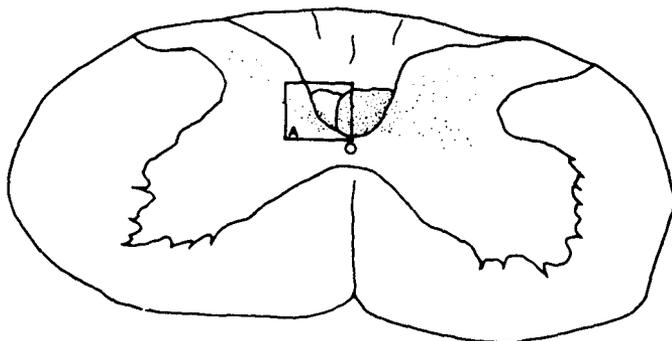


A. CERVICAL LEVEL - C6

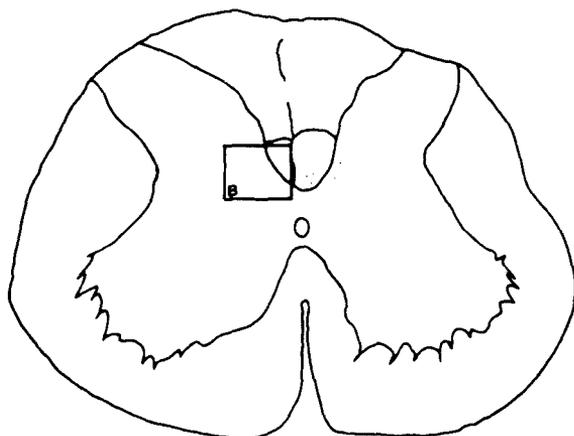


B. LUMBAR LEVEL - L2

Fig. 11. Camera lucida drawings through cervical (A) and lumbar (B) levels of the spinal cord demonstrating the distribution of degenerating axons observed using the Fink-Heimer stain after an adult forelimb motor cortical lesion in the spared hemisphere of an animal which sustained a neonatal SMC lesion. Boxes labeled A and B correspond to photomicrographs in Fig.12.

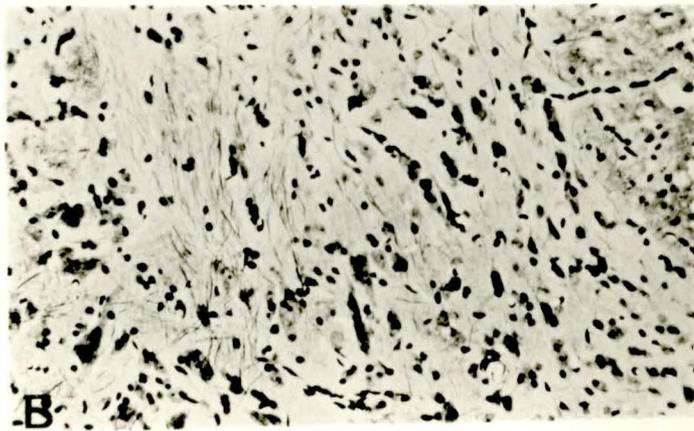
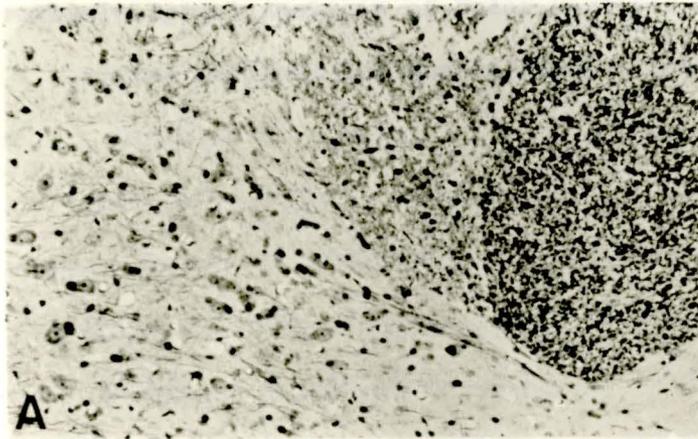


A. CERVICAL LEVEL - C6



B. LUMBAR LEVEL - L2

Fig. 12. Photomicrographs corresponding to boxes labeled A and B in Fig.11. Fink-Heimer stain. 280x. A. Degenerating fibers in the ipsilateral gray matter at cervical spinal cord levels. B. Lack of degenerating fibers in the ipsilateral gray matter at lumbar spinal cord levels.



Electrophysiological Analysis of Motor Cortical Plasticity
After Cortical Lesions in Newborn Rats

ABSTRACT

Intracortical microstimulation of the motor cortex in normal adult rats evoked low threshold contralateral forelimb movements and high threshold ipsilateral movements. Ablation of the opposite sensorimotor cortex in adult animals did not alter these thresholds. However, stimulation of the unablated hemisphere in adult rats that sustained unilateral sensorimotor cortical lesions as neonates elicited low threshold ipsilateral forelimb movements that were similar to contralateral movements. These ipsilateral movements may be mediated via aberrant corticofugal pathways which are known to develop following neonatal cortical lesions.

INTRODUCTION

The immature animal is often thought to compensate for central nervous system injuries better than the adult animal (Kennard, 1936, 1938, 1940, 1942; Stewart and Riesen, 1972; Milner, 1974; Teuber, 1975; Burgess, et al., 1982), although clear exceptions have been described (Goldman, 1974; Schneider, 1979; St. James-Roberts, 1981). Similarly, brain damage in the newborn is commonly found associated with the development of aberrant neuronal pathways (see Lund, 1978; Cotman, 1978; Tsukahara, 1981; and Flohr and Precht, 1981 for reviews), and this morphological reorganization has been postulated to contribute to the observed recovery of function following neonatal central nervous system lesions (Goldberger and Murray, 1974; Loesche and Steward, 1977; Goldberger, 1981; Neumann, et al., 1982).

The rodent corticospinal tract, which is generally considered a completely crossed pathway (Brown, 1971), has been shown to develop an ipsilateral component following either unilateral sensorimotor cortical (SMC) ablation (Hicks and D'Amato, 1970, Leong and Lund, 1973, and Castro, 1975) or pyramidotomy (Castro, 1978a), in newborn rats. Light and electron microscopic reports describe this aberrant pathway as terminating in the appropriate areas of the spinal gray matter but on the "wrong" side of the cord (McClung and Castro, 1975 and Leong, 1976a). Other studies using rodents report the appearance of additional anomalous cortico-brainstem projections after neonatal SMC lesions, including anomalous corticorubral (Nah and Leong, 1976),

corticotectal (Leong and Lund, 1973), corticopontine (Leong and Lund, 1973; Castro and Mihailoff, 1983), and corticoreticular (Hicks and D'Amato, 1970; Leong, 1976b) projections.

In search of electrophysiological support for suggested functional implications of aberrant cortical efferent pathways (Hicks and D'Amato, 1970; Castro, 1977), the present study was undertaken utilizing intracortical microstimulation methods to explore the spared motor cortex of animals sustaining unilateral SMC lesions at two days of age. Our findings consistently demonstrated a significant reduction of threshold currents which elicited ipsilateral forelimb movements in these experimental animals in comparison to adult lesion and unoperated control groups.

A preliminary account of these results has previously appeared in abstract form (Kartje-Tillotson, et al., 1982 and Castro, et al., 1982).

MATERIALS AND METHODS

Subjects

A total of 24 Long-Evans, black hooded rats were divided into three groups: (1) adult animals that had sustained neonatal unilateral SMC lesions (n=10), (2) adult animals sustaining unilateral SMC lesions (n=6), and (3) adult unoperated controls (n=8).

Neonatal Cortical Ablation

Using two day old pups that were anesthetized by hypothermia, the cranium was exposed with a midline skin incision and the skull overlying either the right or left frontal cortex was removed with forceps. The dura was opened using small forceps and a #11 scalpel blade, and the SMC region was aspirated by mild suction with a small pipette. The wound was then packed with gelfoam and the skin sutured together. The pups were warmed under an incandescent lamp, returned to their mothers until weaning and then housed individually until used in the electrophysiological study at 3-5 months of age (although one animal was 11 months old at the time of cortical stimulation).

Adult Cortical Ablation

Adult rats at three months of age were placed under sodium pentobarbital (40mg/Kg) anesthesia and received a single dose of atropine sulfate (.05mg). Animals were placed in a stereotaxic

headholder; the skull was exposed with a midline skin incision, and the bone over either the right or left frontal cortex was removed. The dura was opened and the SMC cortical region was removed with suction. The wound was packed with gelfoam, the skin sutured together, and the animals were returned to their cages until electrophysiological analysis 4-5 months later.

Cortical Stimulation Procedures

Using intraperitoneally administered ketamine hydrochloride (100mg/Kg) anesthesia, with supplemental doses of 20mg/Kg given as needed to prevent spontaneous movements, animals were secured in a stereotaxic headholder while resting on a narrow heating pad. Rectal temperature was monitored and maintained at 36-38 degrees C. The hair on the shoulders and forelimbs was clipped and the limbs were allowed to hang free to better facilitate observation of movements. Prior to opening the skull, the cisterna magna was opened and drained to reduce swelling of the cortex. In animals which had previously sustained unilateral cortical ablation as neonates or as adults, the spared frontal cortical surface was exposed; in normal animals, either the right or left cortex was exposed. The overlying dura was left intact and the brain was further protected with warm mineral oil. A sharpened, glass insulated tungsten wire with a 100 micron tip served as the stimulating electrode. Using bregma as a reference point and utilizing the maps of Hall and Lindholm (1974) and Neafsey and Sievert (1982), the cortical forelimb area was explored in 0.5mm steps in both

a medio-lateral and rostral-caudal direction. Larger or smaller intervals were often used to avoid blood vessels on the cortical surface. The stimulation current (5-100 uamps) was applied with a frequency of 350hz in 300msec trains and 0.25msec pulses, at a depth of 1.7mm. Stimulus currents were monitored on an oscilloscope by measuring the voltage drop across a 10,000 ohm resistor.

The number of points stimulated varied from 14 to 25 per animal, with the majority of points being confined to the forelimb area. Each point was stimulated several times in an increasing and decreasing sequence of current intensities in order to determine the threshold current needed to produce a visible movement. For each stimulus point which evoked a forelimb movement, the contralateral forelimb threshold was found first, and then the ipsilateral threshold was determined. Two investigators collaborated in observing the evoked movements, and for all forelimb points the type of movement was also recorded, i.e., elbow flexion, wrist extension, etc.

An additional 7 animals (2 adult unoperated controls and 5 adult animals sustaining neonatal SMC lesion) were subjected to spinal cord lesions following cortical stimulation. A laminectomy was performed to expose the cervical spinal cord segments. The vertebral spine of C7 was clamped and held rigid to lessen pulsations of the cord. In control animals electrolytic lesions (2.5 milliamps for 5 seconds) were made at level C4 in the corticospinal tract contralateral to cortical stimulation. In neonatal cortical lesion animals either electrolytic lesions (n=3) or lesions made with a #11

scalpel blade (n=2) were placed at level C4 in the corticospinal tract ipsilateral to cortical stimulation. Both immediately prior to and at various intervals after the spinal cord lesions, the forelimb motor cortex was stimulated in order to determine the effect of the lesion on forelimb threshold levels.

At the completion of the experiment, all animals were overdosed with sodium pentobarbital and perfused through the heart with saline followed by 10% buffered formalin. Brains were removed, photographed, and some frozen sectioned at 30-40 microns and stained with either cresyl violet or thionin to facilitate inspection of the cortical lesions. Spinal cord segments at the level of the lesions were removed and frozen sectioned at 40 microns, and stained with either thionin or cyanine-R/neutral red. Sections containing the largest lesions were traced with a drawing tube attachment.

Data Analysis

Stimulation points were selected for statistical analysis according to two criteria: firstly, the evoked contralateral and ipsilateral movements had to be clear cut forelimb responses, with no other body part moving at the observed forelimb thresholds; and secondly, the contralateral threshold had to be equal to or below 30 uamps, and the ipsilateral threshold had to be equal to or below 100 uamps.

Since depth of anesthesia is known to effect threshold values, we used the difference between ipsilateral and contralateral

thresholds in our statistical analysis to control for fluctuations in the animal's level of anesthesia throughout the experiment. Within each animal, the mean difference between contralateral and ipsilateral thresholds was computed by averaging the differences between these thresholds at each stimulation point. Then the overall mean difference in thresholds was computed for the control and experimental groups, and a Student's t-test was used to determine whether this difference was significantly lower in experimental groups as compared to controls.

RESULTS

Cortical Lesion Analysis

The extent of cortical ablations for both adult and neonatal lesion groups are demonstrated in Fig. 1. A coronal section through the midportion of a representative adult SMC lesion is shown in Fig. 2a, while Fig. 2b illustrates a coronal section through the SMC lesion of a typical neonatally ablated animal. Lesions extended through all layers of cortex and in most cases damaged the underlying white matter, as well as the caudate-putamen.

Cortical mapping

Points representing cortical penetrations were plotted on outline drawings depicting the rostral portion of the left cerebral hemisphere. Representative maps are shown for control (Fig. 3a), adult lesion (Fig. 3b), and neonatal lesion (Fig. 3c and 3d) animals. All groups displayed a similar topographical arrangement with two distinct forelimb areas separated by 1-2 mm. Trunk and hindlimb movements were commonly evoked from more caudally placed stimulation points, while neck movements were often found in between the two forelimb areas. Movements of the vibrissae were elicited from medially located stimulation points, and jaw movements were reliably found just lateral to the rostral forelimb area. Although a similar topographical arrangement of cortically evoked movements was seen among all groups, two out of the six animals in the neonatal lesion

group showed a positional shift in the stimulation map; in one animal the entire map was shifted 2 mm caudally (Fig. 3c), and the other animal showed a slightly more rostral representation (Fig. 3d). However, it is unclear if this represents a true cortical reorganization or merely a shift in the location of bregma, since the bones of the skull were obviously disrupted when making the neonatal lesion. As shown in Fig. 3, in all three groups the resulting contralateral and ipsilateral response from one stimulation point were often not the same movement, i.e., the contralateral wrist could be extending while the ipsilateral elbow could be flexing. The majority of movements elicited involved the elbow and wrist joints, although shoulder and digit movements were also frequently observed. Also, there was no apparent change in the types of movements elicited in the neonatally ablated animals as compared to controls, i.e., movements in the shoulder, elbow, wrist, and digits were found in all three groups. Additionally, stimulation in the caudally placed forelimb region tended to evoke more shoulder, elbow, and wrist movements as opposed to the rostrally placed forelimb area where more digit movements were found. These results are in close agreement with recent findings concerning the two forelimb motor areas in the rat frontal cortex (Neafsey and Sievert, 1982).

Effects of Cortical Lesions on Thresholds for Forelimb Movements

As illustrated in Fig. 4, stimulus thresholds for contralateral forelimb movements remained statistically the same for all three

groups. Likewise, stimulus thresholds for ipsilateral forelimb movements were not significantly different in unoperated control and adult lesion groups. However, ipsilateral forelimb thresholds were found to be lower in the neonatal lesion group as compared to adult lesion animals and unoperated controls ($p < .0005$). Consequently, the mean difference (ipsilateral-contralateral thresholds) was also found to be lower in the neonatal lesion group as compared to adult lesion or unoperated control groups ($p < .0005$).

Effects of Corticospinal Tract Ablation on Thresholds for Forelimb Movements

In normal control animals ($n=2$), electrolytic lesion of the corticospinal tract contralateral to cortical stimulation resulted in no response of the contralateral forelimb to cortical stimulation at or below 100 uamps. Ipsilateral forelimb movements remained at normal threshold values. In animals sustaining neonatal SMC damage ($n=3$), lesion of the aberrant ipsilateral corticospinal tract resulted in no response of the forelimb ipsilateral to cortical stimulation at or below 100 uamps. The forelimb contralateral to cortical stimulation demonstrated slightly increased thresholds. Since the aberrant ipsilateral corticospinal tract is a small pathway, it was difficult to restrict lesions to just this structure. Consequently, varying amounts of damage were found in the contralateral corticospinal tract, in parts of the lateral funiculus, as well as in the surrounding gray matter.

DISCUSSION

The present study demonstrates a significant change in the output of the spared, unablated motor cortex of rats sustaining neonatal cortical lesions. Specifically, stimulus currents required to elicit ipsilateral forelimb movements were significantly decreased in these animals in comparison to controls. In contrast, ipsilateral forelimb thresholds for animals which sustained unilateral cortical lesions in adulthood did not decrease in value, remaining at control levels.

The electrophysiological changes observed after neonatal cortical lesions suggest a correlation with previous anatomical studies which describe the development of anomalous corticofugal projections following unilateral neonatal cortical lesions in rats. Rather than the normal, primarily unilateral distributions, the spared, unablated cerebral hemisphere forms bilateral connections with various motor areas, such as the red nucleus (Nah and Leong, 1976), the tectum (Leong and Lund, 1973), the basilar pontine nuclei (Leong and Lund, 1973; Mihailoff and Castro, 1981; Castro and Mihailoff, 1983), and the caudal medullary reticular formation (Hicks and D'Amato, 1970; Leong, 1976b). Additionally, the development of an aberrant ipsilateral corticospinal tract has been well established (Hicks and D'Amato, 1970; Leong and Lund, 1973; Castro, 1975; McClung and Castro, 1975). Anomalous corticospinal fibers deflect at the pyramidal decussation and instead of crossing the midline continue

ipsilaterally into the spinal cord to terminate in the dorsal horn and intermediate gray at both cervical and lumbar levels. Although less dense in comparison to the normal contralateral pathway, this aberrant projection appears to innervate neurons deprived of their normal input due to the neonatal cortical lesion.

Further studies have demonstrated that the ipsilateral corticospinal tract develops in response to cortical lesions in animals up to 17 days of age but not after lesions in older animals (Hicks and D'Amato, 1975; Leong, 1976b). Additional timing studies of corticobulbar sprouting have produced similar results. Corticorubral sprouting only occurred after lesions in rats less than 10 days of age (Nah and Leong, 1976a), and corticoreticular sprouting only occurred up to 17 days of age (Leong, 1976b). While some corticopontine sprouting was still apparent when lesions were made at 20 days of age but not after adult lesions (Leong, 1976), the possibility of corticopontine sprouting after adult lesions is not clearly resolved (Mihailoff, personal communication). In all but possibly this latter case, the ability of cortico-efferent pathways to form new connections in response to injury appears to be restricted to young, pre-weanling ages. This lack of anatomical remodeling in older ages is in agreement with results from the present study which describe no change in ipsilateral forelimb thresholds after lesions in adult animals.

The reported corticospinal tract remodeling suggests that the spared, unablated cerebral cortex may function bilaterally to compensate for lesions of the other hemisphere. Although the rodent

corticospinal tract has been suggested to serve a sensory function based on its terminations in the dorsal horn (Brown, 1971), medullary pyramidotomy was shown to disrupt discrete digital usage (Castro, 1972; Kalil and Schneider, 1975), thereby indicating a prominent role of the rodent corticospinal tract in motor control. In order to determine the possible role of the aberrant corticospinal tract in mediating the evoked ipsilateral forelimb movements observed in this study, experiments were conducted to ablate selectively the ipsilateral corticospinal tract to possibly abolish the low threshold ipsilateral forelimb movements. Although lesion of the aberrant corticospinal tract did appear to affect threshold values for ipsilateral forelimb movements, the data are difficult to interpret since lesions usually included other structures besides the aberrant tract. Future studies are planned to ablate the aberrant tract at the level of the medullary pyramid in an attempt to obtain a more localized lesion.

Studies in the visual system have reported the development of anomalous bilateral cortico-tectal connections after unilateral ablation of the visual cortex in neonatal rats (Mustari and Lund, 1976), or hamsters (Rhoades and Chalupa, 1978). Further electrophysiological experiments in hamsters have demonstrated that the aberrant cortical pathway from the spared visual cortex establishes functional contacts in the contralateral superior colliculus (Rhoades, 1981). Additional studies demonstrate that unilateral removal of the telencephalon in neonatal rats results in

the development of a crossed corticothalamic projection from the spared hemisphere (Neumann, et al., 1982). The appearance of this aberrant pathway was correlated with the functional recovery from lesion-induced behavioral asymmetries, i.e., the cessation of spontaneous turning behavior.

In the present investigation, bilateral forelimb movements following cortical stimulation were almost always observed even in control animals. Hall and Lindholm (1974), using intracortical microstimulation in normal rats, reported some bilateral movements at high current intensities, particularly of the face; however, unlike our findings, no bilateral forelimb responses were reported. Our results are in agreement with an earlier physiological study by Elger, et al. (1977), who described bilateral responses in rodent cervical motoneurons following unilateral epicortical stimulation. Similarly, a recent behavioral study (Price and Fowler, 1981), reported bilateral forelimb deficits in rats subjected to adult unilateral cortical lesion. The results of earlier morphological investigations in the rat have suggested that a normal ipsilateral corticospinal tract may exist (Goodman, et al., 1966; Jacobson, 1967) but this has been disputed by Dunkerley and Duncan (1969) and Brown (1971) who describe only a crossed projection. Recently, Vahlsing and Feringa (1980) have reported a normal uncrossed corticospinal tract in the rat which traverses the ventral funiculus. However, terminations of these axons could not be identified in the spinal cord gray matter. The discrepancies between these studies are probably due to differing

tracing techniques and/or evaluation procedures. However, it is still an interesting and unanswered question as to what pathways mediate the normal ipsilateral forelimb movements.

In summary, the present study has provided electrophysiological evidence for enhanced bilateral output of the spared motor cortex following neonatal cortical ablation. Additionally, these findings lend support to the possible role of cortical efferent remodeling in recovery of motor function following damage to the developing brain.

Acknowledgements

This research was supported by USPHS Grants NS 13230 and NS 16146 from the National Institutes of Health.

Fig. 1. Dorsal view of a rat brain depicting the extent of the cortical lesions in the adult lesion group (a) and the neonatal lesion group (b). Slanted lines show the largest lesion and cross hatching represents the smallest lesion. Cortical damage for all other animals was intermediate between these two extremes and always included the area of the smallest lesion.

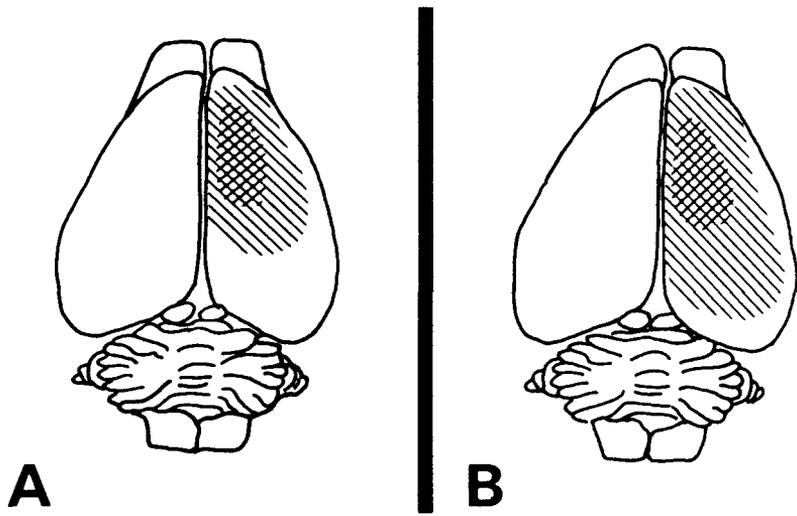


Fig. 2. Representative coronal sections through cortical lesion sites from the adult lesion group (a) and the neonatal lesion group (b). Nissl stain.

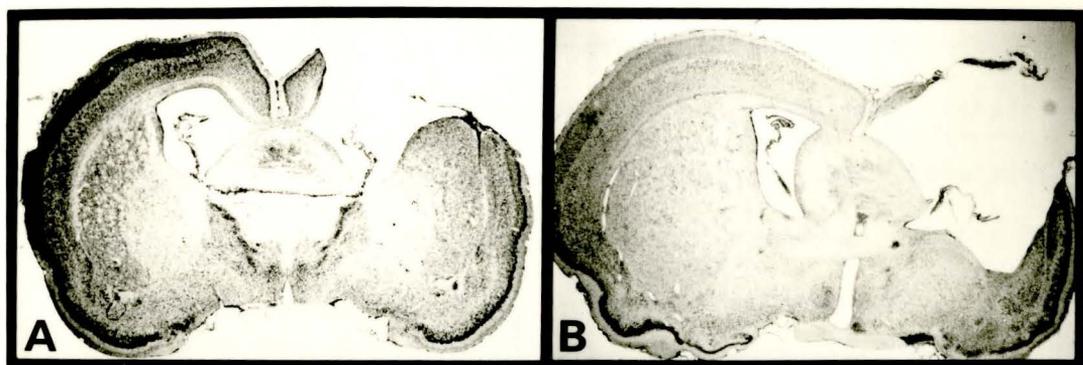


Fig. 3. The results from four stimulation mapping experiments including control (a), adult lesion (b), and neonatal lesion (c and d) animals. Asterisks denote points which were used for statistical analysis. For stimulation points where both contralateral and ipsilateral movements were evoked, the contralateral movement is displayed above the ipsilateral movement. B denotes bregma. Sr=shoulder retraction; Sad=shoulder adduction; Ef=elbow flexion; Wf=wrists flexion; We=wrists extension; Df=digit flexion; Jo=jaw open; V=vibrissae; N=neck; T=trunk; HL=hindlimb; nr=no response. See the text for more details.

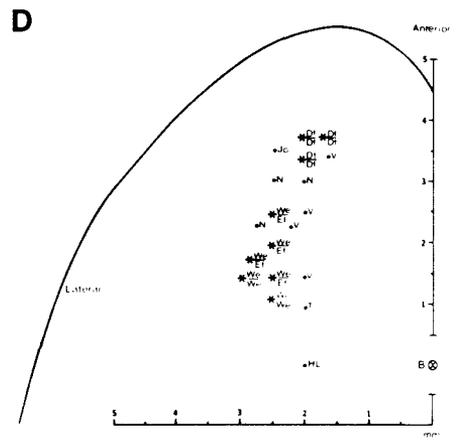
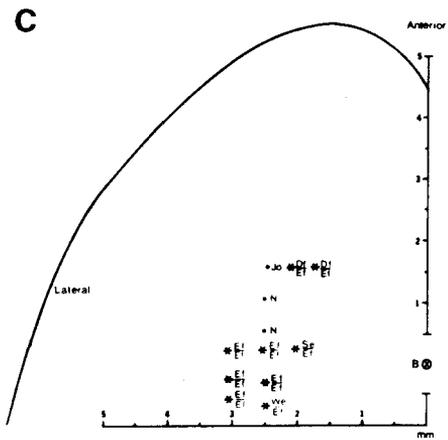
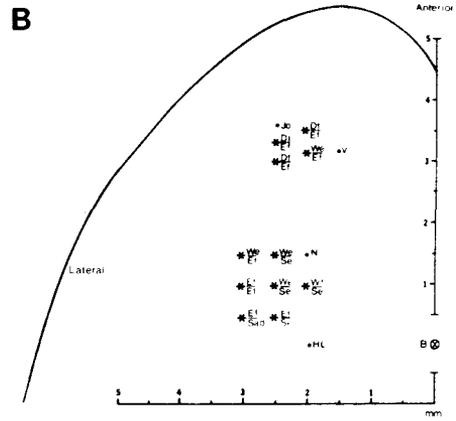
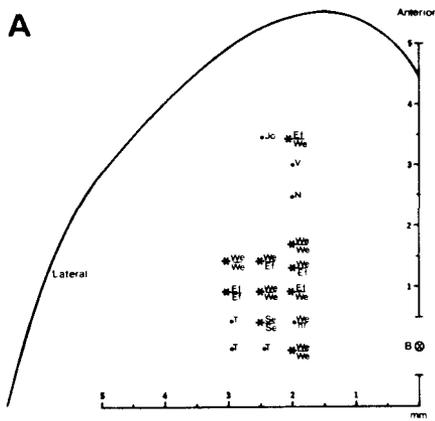
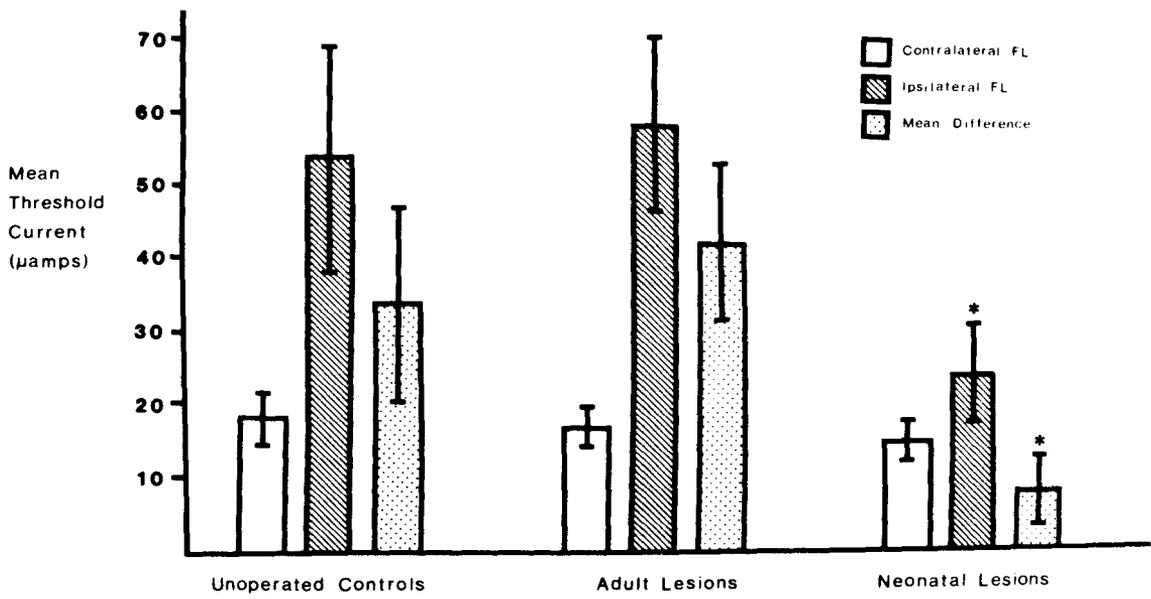


Fig. 4. Histogram demonstrating forelimb responses following cortical stimulation for normal unoperated controls (n=6), adult lesion animals (n=6), and neonatal lesion animals (n=6). Astericks indicate statistical significance at the .0005 level.

•



Limb Preference After Unilateral Pyramidotomy
in Adult and Neonatal rats

ABSTRACT

As previously reported, unilateral pyramidotomy in newborn rats results in the development of an aberrant ipsilateral corticospinal tract that originates from the intact side. In the present study, limb preference after unilateral pyramidotomy in adult and neonatal rats was examined in search of differences that might correlate with this aberrant tract. However, no significant differences were observed between the two groups. Postoperatively, adult animals preferred the limb corresponding to the intact corticospinal tract in spite of a pre- and postoperative testing bias toward the opposite limb. Similarly, the animals that sustained neonatal lesion followed by testing at maturity also preferred the limb corresponding to the normal crossed corticospinal tract.

INTRODUCTION

It is well established that lesions of the central nervous system may result in the development of anomalous neural connections. Such neuroanatomical remodeling has been reported to occur in several systems, including the motor system, and occurs most prominently in response to neonatal lesions (Hicks and D'Amato, 1970; Leong and Lund, 1973; Castro, 1975, 1978; Nah and Leong, 1976a,b; Leong, 1977, 1980; Mihailoff and Castro, 1981; Sonnier, 1982). Although the functional significance of these new connections remains problematic, neuroanatomical remodeling has been thought to provide a partial explanation for the behavioral compensation that often occurs after nervous system lesions. This possible correlation is of particular interest in light of numerous observations that functional recovery, as well as neuroanatomical remodeling, may also be more prominent following brain damage in the newborn.

Recent studies have demonstrated the development of an aberrant ipsilateral corticospinal tract which forms in response to neonatal, unilateral frontal cortical ablation (Hicks and D'Amato, 1970; Leong and Lund, 1973; Castro, 1975) or pyramidotomy (1978) in 1-2 day old rats. Analysis of limb preference after neonatal cortical lesions has provided data which suggests a functional correlation with the aberrant ipsilateral corticospinal tract (Castro, 1977). The present experiment was undertaken to examine this relationship further. Lesions of the pyramid, which are somewhat more specific than the

previously employed cortical lesions, were used with the intention of providing better correlation between the lesions and behavioral data.

METHOD

Animals

Two groups of Long-Evans, black-hooded rats were used in these experiments. The first group consisted of 11 adult rats; 9 of these animals sustained unilateral pyramidotomies and 2 served as operate controls. A second, neonatal group, comprised 19 animals; 13 of which received unilateral pyramidotomies at 1-2 days of age. The other 6 animals served as operate controls.

Surgery and Histology

Adult rats were anesthetized with sodium pentobarbital (40 mg/Kg) and newborn rats by hypothermia. A similar surgical approach was used in both the adults and pups. In both groups a ventral midline incision was made, the sterno-hyoid and sterno-thyroid muscle insertions on the left were sectioned and retracted, and the trachea and esophagus were slightly displaced to the right. Using an operating microscope, blunt deep dissection revealed the outer surface of the occipital bone which was opened with a dental drill. The medullary pyramids (i.e., the corticospinal tracts) were thus exposed and the left pyramid was incised with a sharp No.11 scalpel blade. The esophagus and trachea were replaced, the muscles sutured, and the skin closed by sutures. Neonatal animals were slowly warmed by an incandescent lamp and returned to their mothers until weaning.

After behavioral testing, animals were sacrificed by an

overdose of sodium pentobarbital and perfused through the heart with saline followed by 10% buffered formalin. The brains were removed, fixed in formalin, and photographed. They were subsequently embedded in paraffin, sectioned at 10 microns and stained with luxol fast blue/cresyl violet. Camera lucida drawings were made of the pyramidal tract lesions, and planimetric methods were employed to estimate the extent of the lesions using the right, unablated pyramid as a reference control.

Testing Apparatus and Procedures

As in a previous study (Castro, 1977), animals were tested for limb preference in a rectangular (20x29x30 cm) plexiglass chamber. A small opening approximately 2 cm in diameter was made in the front wall adjacent to the right side wall of the chamber, and a food tray was attached outside of the chamber directly under this opening. The animals were required to extend a forelimb through the opening in order to obtain small food pellets (Noyes, 45 mg). Although it was possible for the animal to use either forelimb, the placement of the opening next to the right chamber wall biased the animal to use the right limb. Bias for the right limb corresponded to the left medullary pyramidotomy since the corticospinal tracts decussate below the level of the lesion.

The adult lesion group received both pre- and postoperative testing. Prior to testing, animals were reduced to about 80% of their body weight by maintaining them on a restricted diet for several days.

They were then placed in the testing chamber for 1-2 hours a day for 2-3 days or until they learned to reach through the opening for food. At this time testing was begun. A single rat was placed in the chamber and forelimb attempts through the opening were observed and recorded in terms of the limb used. An attempt was defined as any time a rat extended its entire forelimb through the opening. Fifty attempts comprised each daily testing session, and the testing lasted from 4-11 days. At the completion of preoperative control testing, 9 of the 11 rats underwent unilateral pyramidal tract section. At approximately 10 days postoperatively, rats were again tested for limb preference.

Animals in the neonatal lesion group which sustained pyramidal tract section at 1-2 days of age were tested at approximately 2-4 months of age using the same test procedure as were rats that sustained adult pyramidotomy.

RESULTS

Adult Lesion Group

The pre- and postoperative data for the final 100 attempts of limb preference testing obtained from animals that sustained unilateral pyramidotomy as adults are presented in Fig.1. The arrow at the top of the figure indicates the direction of testing bias, as determined by the testing chamber. The figurines at the right of the figure indicate the crossed distribution of the corticospinal tracts and show the lesion rostral to the decussation. Preoperatively, all animals preferred (mean=93.2%) to use the right limb which corresponded to the testing bias. Postoperatively, the 2 control animals continued to use this same limb. However, 8 of the 9 animals with pyramidal tract lesions switched limb preference against the testing bias and preferred to use the left limb (ipsilateral to the lesion and corresponding to the intact corticospinal tract). Since postoperative scores and the extent of pyramidal tract lesions were not uniform, the data were not combined but are presented individually for each animal in Fig.1. The estimated amount of sparing of the ablated corticospinal tract is included in parentheses next to each animal number. Inspection for damage to structures in proximity to the pyramids, e.g. the medial lemniscus, revealed no correlation with postoperative performance. In fact, 5 animals sustained only partial pyramidotomies by lesions confined to within the pyramids; yet these animals still showed a postoperative switch in limb preference. A

representative adult pyramidal tract lesion is presented in Fig.2A.

Neonatal Lesion Group

A summary of the limb preference testing for the animals that sustained neonatal pyramidal tract section is presented in Fig.3. Similar to the adult lesion group, 11 of 13 animals preferred (mean=98.3%) to use the left limb which was ipsilateral to the lesion and which corresponded to the normal crossed pyramidal tract. Of the 2 animals that preferred the right limb in accordance with the testing bias, lesion analysis revealed pyramidal tract sparing of approximately 7 and 40%. All remaining animals had a complete or nearly complete unilateral pyramidotomy (Fig.2B). Control animals preferred (mean=91.0%) to use the right limb which corresponded to the testing bias.

DISCUSSION

The present study indicates that unilateral pyramidotomy in adult rats results in a preference for the limb ipsilateral to the side of the lesion and which also corresponds to the intact corticospinal tract. These animals demonstrate a postoperative switch in limb preference against both a pre- and postoperative testing bias. These results are in agreement with previous findings (Castro, 1977) in which unilateral frontal cortical ablation in adult rats also resulted in a preference for the limb corresponding to the intact corticospinal tract. Additionally, the results are supportive of an earlier study of limb preference (Peterson and Fracarol, 1938), which implicated a small region of the contralateral frontal cortex (and therefore presumably the corticospinal tract) in the control of handedness in rats.

Studies of limb preference after corticospinal tract lesions in monkeys have also been reported. For example, unilateral section of the cerebral peduncle resulted in a preference for the limb corresponding to the intact side (Bucy, et al., 1966). Similarly, monkeys with unilateral pyramidotomy preferred the unaffected limb, and those with bilateral pyramidotomy preferred the limb corresponding to the tract with the greatest amount of sparing (Lawrence and Kuypers, 1968). These data support our findings that even with 71% sparing of the ablated pathway animals preferred the limb corresponding to the completely intact tract.

Additional studies concerning corticospinal tract function have demonstrated that pyramidotomy in adult monkeys disrupts discrete digital usage (Tower, 1940; Lawrence and Kuypers, 1968; Beck and Chambers, 1970; Laursen, 1971; Woolsey, et al., 1972). Similar deficits of digital usage have also been described after pyramidal tract lesions in adult rats (Castro, 1972), opossums (Hore, et al., 1973), and hamsters (Kalil and Schneider, 1975). Such reports pertaining to digital usage are considered most relevant to the present study of limb preference. In the early postoperative period after adult pyramidotomy, most animals in our study showed a right limb preference. This preference was in accordance with testing bias and corresponded to the ablated corticospinal tract. However, in agreement with earlier studies, usage of this limb was markedly impaired in comparison to preoperative testing, and within 5 testing sessions animals switched preference in favor of the left limb which corresponded to the intact tract. Accordingly, the postoperative switch in limb preference is likely due to the loss of digital skill after unilateral pyramidotomy and may simply manifest a preference for the more skillful limb. The initial postoperative use of the less skillful limb is attributed to a postoperative perseveration caused by preoperative conditioning.

Histological analysis of adult pyramidotomies revealed considerable variation in the amount of the pathway spared among animals (approximately 4-71% sparing). However, sparing showed no correlation with the rate and extent of limb preference switching. In

fact, it is considered noteworthy that 3 animals with considerable sparing (approximately 64, 69, and 71%) nonetheless switched preference in favor of the intact pathway. The single animal that failed to switch limb preference in spite of only 18% tract sparing is unexplained by the data.

The second group of rats which sustained unilateral pyramidotomy at 1-2 days of age performed similarly to animals with adult lesions. When tested as adults, the neonatal lesion group also preferred to use the left limb (corresponding to the intact crossed pyramidal tract) in spite of a testing bias for the opposite limb. However, unlike the adult group these animals showed an immediate testing preference for the limb which corresponded to the intact corticospinal tract. The differences between the 2 groups in the early postoperative testing periods are partially attributed to the lack of preoperative training for the neonatal group and therefore the absence of postoperative perseveration as seen in the adult lesion group. Additionally, growth and maturation after neonatal pyramidotomy may have caused animals to develop a strong limb preference corresponding to the unablated crossed corticospinal tract, and this strong preference was unaffected, even in initial testing, by the testing bias.

The 2 animals in the neonatal group that preferred the limb biased by testing had approximately 7 and 40% sparing of their corresponding pyramids. Although it is difficult to reconcile the data relevant to the animals with lesser sparing, the rat with 40%

sparing may have had enough of the tract remaining to develop sufficient dexterity to prefer the corresponding limb. It must also be presumed that the early age at the time of the lesion was critical considering that 40% or more sparing of the pyramidal tract in animals in the adult lesion group caused animals to switch limb preference.

In summary, this study revealed no consistent behavioral differences, as measured by limb preference, between adult rats that sustained pyramidal tract lesion at adult or neonatal ages. Accordingly, we found no behavioral support for the efficacy of the aberrant, ipsilateral corticospinal projections that develop after unilateral pyramidotomy in rats (Castro, 1978). Whereas the ipsilateral corticospinal tract also develops after neonatal frontal cortical lesion (Hicks and D'Amato, 1970; Leong and Lund, 1973; Castro, 1975), the present findings contrast previous studies of limb preference which did suggest a functional correlation with the ipsilateral tract after neonatal cortical lesions (Castro, 1977). The use of more restricted lesions in the present experiment, i.e., pyramidotomy versus large cortical lesions, did not reveal a better functional correlation with the corticospinal tract as was initially hypothesized. Possibly, the remodeling of corticopontine and corticorubral connections, which occurs in addition to corticospinal remodeling after neonatal cortical lesions (Leong and Lund, 1973; Nah and Leong, 1976a,b; Leong, 1978; Mihailoff and Castro, 1981; Sonnier, 1982; Castro and Mihailoff, 1983), but has not been described after pyramidal lesions, may significantly contribute to the behavioral

compensation previously observed after cortical lesions. The extensive remodeling of motor system pathways in response to neonatal frontal cortical lesions may alter related descending systems sufficiently to "support" the relatively small aberrant ipsilateral corticospinal tract and thereby enable it to be "functionally competitive" with the normally innervated side.

Fig. 1. Limb preference testing scores for animals that received adult pyramidal tract lesions. Scores are derived from the final 100 attempts of pre- and postoperative testing. Although the preoperative data are grouped, the postoperative scores are presented in individual bars for each animal because of the variability in pyramidal tract lesions. The numbers above the bars indicate animal number and the amount of pyramidal tract sparing is in parentheses. The criterion for limb preference was arbitrarily defined at 2 standard deviations below the mean preoperative level of testing (i.e., approximately 75). Testing bias was toward the limb contralateral to the lesion. The level of the lesion and the laterality of the pyramidal tracts are indicated by the figurines on the right.

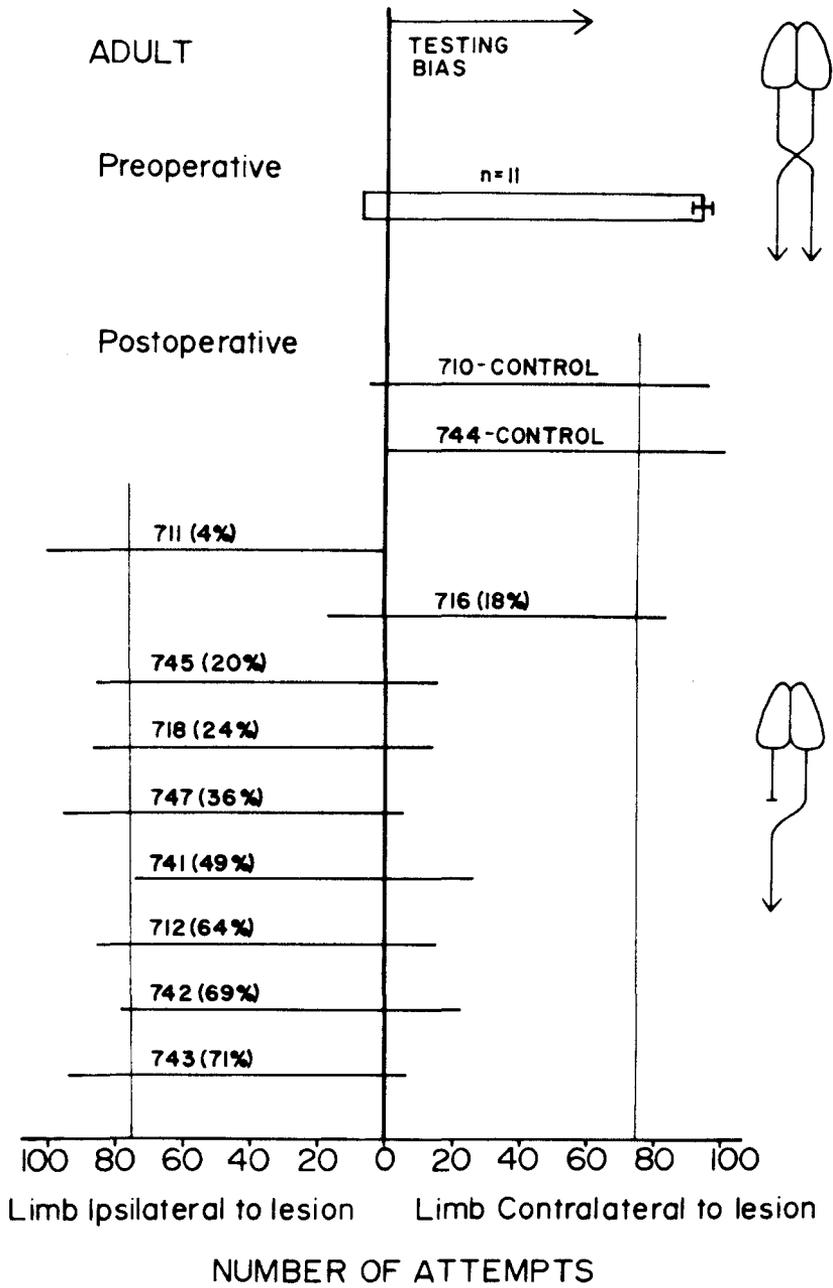


Fig. 2. Representative photomicrographs through medullary brainstem levels from adult rats that sustained adult (A) or neonatal (B) pyramidal tract lesions. 15x. Luxol fast blue/cresyl violet stain. PT, pyramidal tract.

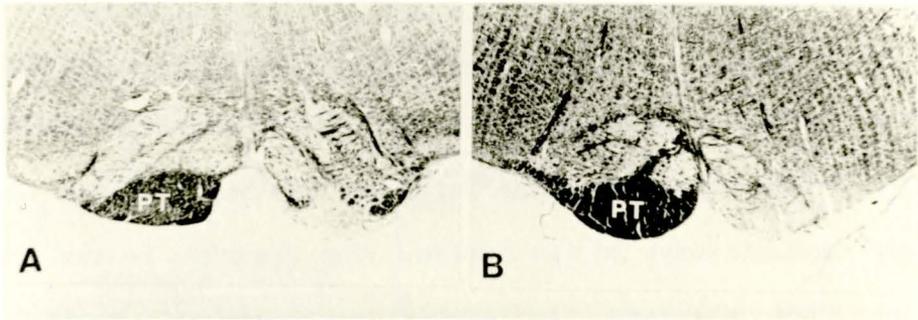
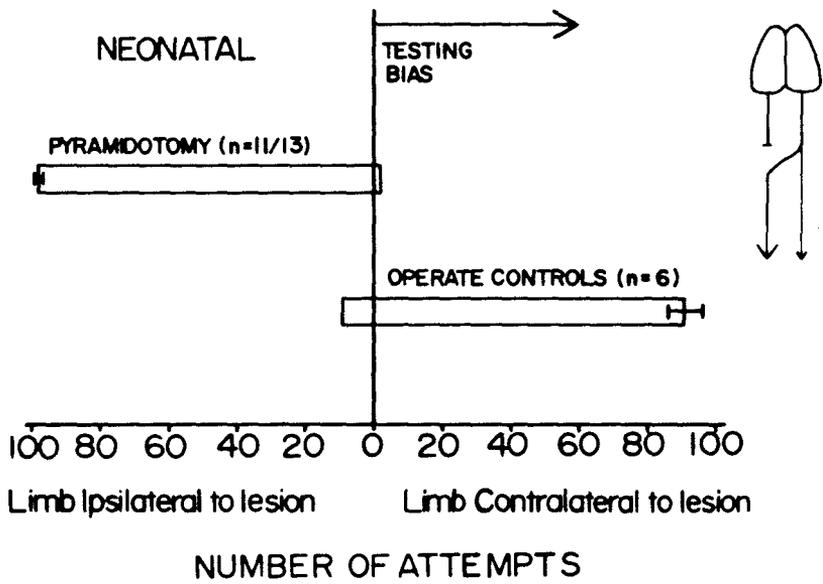


Fig. 3. Postoperative testing scores for animals that sustained neonatal unilateral pyramidotomy and were tested at maturity. Controls received neonatal sham surgery. Testing bias was toward the limb contralateral to the lesion. The figurine to the right includes the aberrant ipsilateral corticospinal tract that develops in response to neonatal pyramidotomy.



GENERAL DISCUSSION

The mammalian CNS can no longer be viewed as a static structure; rather, the CNS is capable of dramatic neuroanatomical remodeling following injury. Due to the voluminous reports documenting the formation of anomalous connections, the concept of neuronal plasticity has now been firmly established in the neuroscientific literature. The ability of the CNS to alter its connections in response to injury raises questions concerning the functional consequences of such remodeled projections. Various studies have implicated anomalous pathways with recovery of function (Hicks and D'Amato, 1970; Devor, 1975; Castro, 1977; Labar, et al., 1981). However, the functional significance of anomalous pathways is still not clear. The influential studies of Schneider (1970, 1973, 1979) analyzed the effects of neonatal tectal lesions on visually guided behavior in hamsters. These animals displayed unusual responses in that presentation of sunflower seeds in the upper visual field resulted in head turning away from the stimulus rather than towards it. The anomalous retinotectal fibers which recrossed the midline to terminate in the spared tectum were apparently mediating this maladaptive type of behavior. The investigations of Schneider were important in that anomalous growth was directly linked with detrimental behavior.

Due to the discrepancies in the literature regarding the functional significance of anomalous pathways, the studies included in this dissertation attempted to seek functional correlations for anomalous cortico-efferent projections. The first study determined that anomalous corticopontine and corticospinal fibers distributed in an ordered, topographic manner. Similar types of topographic distributions have been documented for anomalous pathways in the visual system. Mustari and Lund (1976) showed anatomically that anomalous corticotectal fibers distributed in an orderly fashion in the contralateral superior colliculus by synapsing topographically only in laminae appropriate for this visual pathway. Anomalous retinofugal fibers have also been shown to distribute topographically (Cunningham and Speas, 1975; Finlay, et al., 1979; Frost and Schneider, 1979), as well as aberrant pathways in the limbic system (Steward, 1976).

The somatotopic distribution of anomalous fibers implies that such aberrant growth obeys the same rules which govern normal developing axons. Axonal-target interactions may be influenced by an inherent tendency for neurons to conserve a total amount of terminal arborizations, as first proposed by Schneider (1970, 1973). Additionally, competition with other fibers for terminal space probably plays a role in establishing permanent connections, as shown in the normal developing visual system (Hubel and Wiesel, 1965). Crain and Hall (1981) have noted competition between afferents for synaptic space in the lateral posterior thalamic nucleus of the

hamster both normally and following tectal lesions. A clear example of exclusion of one fiber system by another is shown in the septal nucleus of the rat. If the input from one fimbria is removed, the other fimbria expands its terminal field to fill the deafferented region entirely (Field, et al., 1980). However, if both fimbria are cut, then a third, as yet undetermined fiber system reinnervates the septal nucleus (Raisman, 1977). Through studies on the hippocampus, it now appears that one afferent fiber system may actually control the distribution pattern of the remaining inputs to a particular brain region; the so-called "critical afferent" theory (Cotman, et al., 1981). Since anomalous fibers have been shown to form topographical connections in sites functionally similar to their normal termination zones, perhaps aberrant fibers have a competitive advantage in such regions, as suggested by Zimmer (1974).

In reference to the present work, the specificity of remodeled corticopontine and corticospinal projections, as opposed to a random, non-specific growth, suggests that these pathways may be of functional significance to the animal. In order to test this hypothesis further, a physiological study was undertaken which disclosed that following neonatal cortical removal the spared hemisphere functioned bilaterally in the control of forelimb movements. In order to determine the anomalous corticofugal pathway which was actually mediating the abnormal ipsilateral response, specific lesions of the aberrant ipsilateral corticospinal tract were attempted. Results showed that interruption of this aberrant pathway at the spinal cord level

abolished forelimb movements due to ipsilateral cortical stimulation, thereby indicating a prominent functional role for the aberrant corticospinal tract. However, due to the difficulty in confining the spinal cord ablations to the small ipsilateral tract, other structures which might have mediated the ipsilateral response were invariably included in these lesions. In future studies the aberrant corticospinal tract will be sectioned at the level of the medullary pyramid in order to obtain a "cleaner" lesion. If low threshold ipsilateral forelimb responses are then present after pyramidotomy, such responses would probably be due to other anomalous pathways which are known to develop after cortical lesion, such as aberrant corticorubral (Nah and Leong, 1976a) or corticoreticular (Hicks and D'Amato, 1970; Leong and Lund, 1973) projections.

The last study in this dissertation was a behavioral investigation undertaken in an attempt to correlate functional sparing with anomalous cortico-efferent pathways. Various studies have indicated that animals sustaining brain lesions as neonates recover better than animals given similar lesions in adulthood (Kennard, 1942; Stewart and Riesen, 1972; Golman and Galkin, 1978; Bregman and Goldberger, 1982). Since the young brain also has a greater capacity for remodeling of central connections as compared to the adult (Scheff, et al., 1980; Nah, et al., 1980), it is tempting to conclude that the anatomical changes found after neonatal lesion are responsible for the observed recovery of function. Previous studies indicated that rats sustaining unilateral cortical lesions as neonates

demonstrated functional sparing of certain locomotor (Hicks and D'Amato, 1970) and limb preference (Castro, 1977) tasks. These studies suggested that the aberrant ipsilateral corticospinal tract may play a role in the observed sparing of function. To test this hypothesis further, in the present investigation animals received unilateral pyramidal tract lesions at newborn or adult ages, since neonatal pyramidotomy results in the development of an anomalous ipsilateral corticospinal tract presumably without the complication of other cortico-efferent remodelling. The results demonstrated that animals with neonatal pyramidal tract lesions did not differ from animals with adult lesions in preferring to use the limb associated with the normal, intact pyramidal tract. The data suggest that the aberrant tract is not capable of competing with the normal corticospinal pathway in terms of limb usage. The actual integrity of the limb supplied by the aberrant ipsilateral tract could be further tested by forcing the animal to use this limb and consequently evaluating motor performance. Preliminary data suggest that when tested in such a way, the aberrantly innervated forelimb is capable of some degree of manipulatory skill.

In conclusion, the experiments in this dissertation support the possibility that aberrant cortico-efferent connections play an important functional role in the brain damaged animal. The concept that anomalous pathways contribute to recovery after brain damage may be important when considering the human case of patients suffering from brain or spinal cord injury. Considering the many observations

of remodeling in experimental animals, including recent studies on monkeys (Goldman, 1978; Goldman and Galkin, 1978), it is reasonable to assume that neuronal plasticity is indeed a property of the human brain. Accordingly, it is hoped that the information gained from animal models in regard to the mechanisms of CNS repair will someday benefit patients suffering from neurological damage.

SUMMARY

Neuroanatomical plasticity is defined as the development of anomalous neural connections in response to central nervous system injury. Following unilateral cerebral cortical lesions in newborn rats, the corticopontine projection demonstrates an increase in contralateral projections, while both unilateral cortical lesions and pyramidal tract lesions result in the formation of anomalous ipsilateral corticospinal fibers.

The ability of the central nervous system to alter its connections in response to injury raises questions concerning the functional consequences of such remodeled pathways. The present study investigated the functional implications of anomalous corticopontine and corticospinal projections. Experiments were conducted along three methodological approaches:

Anatomical: To attribute a positive functional role for anomalous pathways implies the formation of new axonal connections in an ordered, precise way. The topographic distribution of anomalous corticopontine and corticospinal pathways was examined in adult rats sustaining neonatal unilateral cortical lesions using two anterograde tracing techniques, autoradiography and degeneration staining. Aberrant cortical efferent fibers distributed in a precise, somatotopic manner into functionally appropriate pontine and spinal

cord areas, supporting the possibility that aberrant cortico-efferent fibers may be functional.

Physiological: Intracortical microstimulation of the motor cortex in normal rats evoked low threshold movements of the limbs contralateral to cortical stimulation, while movements of the ipsilateral limbs occurred with high threshold stimulation currents. In adult rats that sustained neonatal unilateral cortical lesions, low threshold, cortically evoked ipsilateral limb movements were observed. These low threshold ipsilateral limb movements were not found in animals sustaining similar cortical lesions as adults. This study therefore suggests that anomalous cortico-efferent pathways are electrophysiologically active.

Behavioral: Using the behavioral measure of limb preference the possibility of recovery of function in animals sustaining neonatal pyramidal tract lesions as compared to animals given similar lesions as adults was evaluated. The results from this investigation demonstrated that animals with neonatal lesions did not differ from those sustaining adult lesions in terms of the behavioral task measured, and no correlation between the anomalous corticospinal pathway and sparing of function was observed. Further behavioral studies are needed before final conclusions can be drawn.

BIBLIOGRAPHY

- Abdel-Kader, G.A., The organization of the cortico-pontine system of the rabbit, *J. Anat.*, 102 (1968) 165-181.
- Adams, C.E., Parnavelas, J.G., Mihailoff, G.A. and Woodward, D.J., The neurons and their postnatal development in the basilar pontine nuclei of the rat, *Brain Res. Bull.*, 5 (1980) 277-283.
- Albus, K. and Donate-Oliver, F. Cells of origin of the occipito-pontine projection in the cat: functional properties and intracortical location, *Exp. Brain Res.*, 28 (1977) 167-174.
- Albus, K., Donate-Oliver, F., Sanides, D. and Fries, W., The distribution of pontine projection cells in visual and association cortex of the cat: An experimental study with HRP, *J. Comp. Neurol.*, 201 (1981) 175-189.
- Allen, G.I., Korn, H., Oshima, T. and Toyama, K., The mode of synaptic linkage in the cerebro-ponto-cerebellar pathway of the cat. II. Responses of single cells in the pontine nuclei, *Exp. Brain Res.*, 24 (1975) 15-36.
- Asanuma, H., Babb, R.S., Mori, A. and Waters, R.S., Input-output relationships in cat's motor cortex after pyramidal section, *J. of Neurophysiology*, 46 (1981) 694-703.
- Azizi, S.A., Mihailoff, G.A., Burne, R.A. and Woodward, D.J., The pontocerebellar system in the rat: an HRP study. I. Posterior vermis, *J. Comp. Neurol.*, 197 (1981) 543-558.
- Beck, C. and Chambers, W.W., Speed, accuracy and strength of forelimb movements after unilateral pyramidotomy in rhesus monkey, *J. Comp. and Phys. Psych. Mono.*, 70 (1970) 1-22.
- Benjamin, R.M. and Thompson, R.F., Differential effects of cortical lesions in infant and adult cats on roughness discrimination, *Exp. Neurol.*, 1 (1959) 305-321.
- Bentivoglio, M, Kuypers, H.G.J.M., Catsman-Berrevoets, C.E., Loewe, H. and Dann, O., Two new fluorescent retrograde neuronal tracers which are transported over long distances, *Neurosci. Let.*, 18 (1980) 25-30.
- Biber, M.P., Kneisley, L.W. and LaVail, J.H., Cortical neurons projecting to the cervical and lumbar enlargements of the spinal cord in young and adult rhesus monkeys, *Exp. Neurol.*, 59 (1978)

492-508.

Bloedel, J.R. and Courville, J., Cerebellar afferent systems, In: J.M. Brookhart and V.B. Mountcastle (Eds.), Handbook of Physiology - The Nervous System II, Williams and Wilkens Co. Baltimore, 1981, pp. 735-830.

Bodian, D., Origin of specific synaptic types in the motoneuron neuropil of the monkey, J. Comp. Neurol., 159 (1975) 225-244.

Bregman, B. and Goldberger, M., Anatomical plasticity and sparing of function after spinal cord damage in neonatal cats, Science, 217 (1982) 553-555.

Brodal, A. Cerebrocerebellar pathways. Anatomical data and some functional implications, Acta Neurol. Scand., Suppl. 51 (1972) 153-196.

Brodal, A., Neurological Anatomy in Relation to Clinical Medicine, Oxford University Press, New York, 1981.

Brodal, A., Destombes, J., Lacerda, A.M. and Angaut, P., A cerebellar projection onto the pontine nuclei. An experimental anatomical study in the cat, Exp. Brain Res., 16 (1972) 115-139.

Brodal, A. and Hoddevik, G.H., The pontocerebellar projection to the uvula in the cat, Exp. Brain Res., 32 (1978) 105-116.

Brodal, A. and Jansen, J., The ponto-cerebellar projection in the rabbit and cat. Experimental investigations, J. Comp. Neurol., 84 (1946) 31-118.

Brodal, P., The corticopontine projections in the cat. I. Demonstration of a somatotopically organized projection from the primary sensorimotor cortex. Exp. Brain Res., 5 (1968a) 210-234.

Brodal, P., The corticopontine projections in the cat. Demonstration of a somatotopically organized projection from the second somatosensory cortex, Arch. Ital. Biol., 106 (1968b) 310-332.

Brodal, P., The corticopontine projections in the cat. I. The projections from the proreate gyrus, J. Comp. Neurol., 142 (1971a) 127-140.

Brodal, P., The corticopontine projections in the cat. II. The projections from the orbital gyrus, J. Comp. Neurol., 142 (1971b) 141-152.

Brodal, P., The corticopontine projections from the visual cortex in the cat. I. The total projections and the projections from area

- 17, *Brain Res.*, 39 (1972a) 297-317.
- Brodal, P., The corticopontine projections from the visual cortex in the cat. II. The projections from areas 18 and 19, *Brain Res.*, 39 (1972b) 319-335.
- Brodal, P., The corticopontine projections in the cat. The projections from the auditory cortex, *Arch. Ital. Biol.*, 110 (1972c) 119-144.
- Brodal, P., The corticopontine projection in the rhesus monkey. Origin and principles of organization, *Brain*, 101 (1978) 251-283.
- Brodal, P., The pontocerebellar projection in the rhesus monkey: An experimental study with retrograde axonal transport of horseradish peroxidase, *Neurosci.*, 4 (1979) 193-208
- Brodal, P. and Walberg, F., The pontine projection to the cerebellar anterior lobe. An experimental study in the cat with retrograde transport of horseradish peroxidase, *Exp. Brain Res.*, 29 (1977) 233-248,
- Brooks, V.B. and Stoney, S.D., Motor mechanisms: The role of the pyramidal system in motor control, *A. Rev. Physiol.*, 33 (1971) 337-392.
- Brown, L.T., Projections and terminations of the corticospinal tract in rodents, *Exp. Brain Res.*, 13 (1971) 432-450.
- Bucy, P.C., Keplinger, J.E. and Sequeira, E.B., Destruction of the pyramidal tract in man, *J. Neurosurg.*, 21 (1964) 385-398.
- Bucy, P.C., Ladpli, R. and Ehrlich, A., Destruction of the pyramidal tract in the monkey. The effects of bilateral section of the cerebral peduncles, *J. Neurosurg.*, 25 (1966) 1-20.
- Burgess, J.W., Villablanca, J.R., Olmstead, C.E., and Levine, M.S., Differential recovery from hemispherectomy in kittens and cats, *Neurosci. Abst.*, 8 (1982) 746.
- Burne, R.A., Azizi, S.A., Mihailoff, G.A. and Woodward, D.J., The tectopontine projection in the rat with comments on visual pathways to the basilar pons, *J. Comp. Neurol.*, 202 (1981) 287-307.
- Buxton, D.F., and Goodman, D.C., Motor function and the corticospinal tracts in the dog and racoon, *J. Comp. Neurol.*, 129 (1967) 341-360.
- Castro, A.J., Motor performance in rats. The effects of pyramidal

- tract section, *Brain Research*, 44 (1972) 313-323.
- Castro, A.J., Ipsilateral corticospinal projections after large cerebral lesions in neonatal rats, *Exp. Neurol.*, 46 (1975) 1-8.
- Castro, A.J., Limb preference after lesions of the cerebral hemisphere in adult and neonatal rats, *Physiol. Behav.*, 18 (1977) 605-608.
- Castro, A.J., Analysis of corticospinal and rubrospinal projections after neonatal pyramidotomy in rats, *Brain Res.*, 144 (1978a) 155-158.
- Castro, A.J., Projections of the superior cerebellar peduncle in rats and the development of new connections in response to neonatal hemicerebellectomy, *J. Comp. Neurol.*, 178 (1978b) 611-628.
- Castro, A.J. and Mihailoff, G.A., Corticopontine remodelling after cortical and/or cerebellar lesions in newborn rats, *J. Comp. Neurol.*, (1983) in press.
- Castro, A.J., Neafsey, E.J. and Kartje-Tillotson, G., Anatomical and physiological analysis of the aberrant ipsilateral corticospinal tract in rats, *Neurosci. Lett.*, Suppl. 10 (1982) 104.
- Catman-Berrevoets, C.E. and Kuypers, H.G.J.M., Cells of origin of cortical projections to dorsal column nuclei, spinal cord, and bulbar medial reticular formation in the rhesus monkey, *Neurosci. Lett.*, 3 (1976) 245-252.
- Chambers, W.W. and Liu, C-N., Cortico-spinal tract of the cat. An attempt to correlate the pattern of degeneration with deficits in reflex activity following neocortical lesions, *J. Comp. Neurol.*, 108 (1957) 23-55.
- Chan-Palay, V., *Cerebellar Dentate Nucleus: Organization, Cytology, And Transmitters*, Springer-Verlag, New York, 1977.
- Cooper, M.H. and Beal, J.A., The neurons and the synaptic endings in the primate basilar pontine nuclei, *J. Comp. Neurol.*, 180 (1978) 17-42.
- Cooper, M.H. and Fox, C.A., The basilar pontine gray in the adult monkey (*Macaca mulatta*): A golgi study, *J. Comp. Neurol.*, 168 (1976) 145-174.
- Cotman, C.W., *Neuronal Plasticity*, Raven Press, New York, 1978.
- Cotman, C.W., Lewis, E.R., and Hand, D., The critical afferent theory: a mechanism to account for septohippocampal development and plasticity, In: H. Flohr and W. Precht (Eds.), *Lesion-Induced*

Neuronal Plasticity in Sensorimotor Systems, Springer-Verlag, New York, 1981, 13-26.

Cotman, C.W. and Nieto-Sampedro, M. and Harris, E.W., Synapse replacement in the nervous system of adult vertebrates, *Physiol. Reviews*, 61 (1981) 684-784.

Coulter, J.D., Ewing, L.K. and Carter, C.M., Origin of primary sensorimotor cortical projections to lumbar spinal cord of cat and monkey, *Brain Res.*, 103 (1976) 366-372.

Coulter, J.D. and Jones, E.G., Differential distribution of corticospinal projections from individual cytoarchitectonic fields in the monkey, *Brain Res.*, 129 (1977) 335-340.

Cunningham, T.J. and Speas, G., Inversion of anomalous uncrossed projections along the mediolateral axis of the superior colliculus: implications for retinocollicular specificity, *Brain Res.*, 88 (1975) 73-79.

Dalmeida, R.E. and Yu, J., Forelimb movements in cats with complete or partial bulbar pyramid lesions, *Acta Neurobiol. Exp.*, 41 (1981) 509-512.

DeMeyer, W., Ontogenesis of the rat corticospinal tract, *Arch. Neurol.*, 16 (1967) 203-211.

Devor, M., Neuroplasticity in the sparing or deterioration of function after early olfactory tract lesions, *Science*, 190 (1975) 998-1000.

Dhanarajan, P., Ruegg, D.G. and Wiesendanger, M., An anatomical investigation of the corticopontine projection in the primate (*Saimiri sciureus*). The projection from motor and somatosensory areas, *Neurosci.*, 2 (1977) 913-922.

Donatelle, J.M., Growth of the corticospinal tract and the development of placing reactions in the postnatal rat. *J. Comp. Neurol.*, 175 (1977) 207-232.

Doty, R.W., Functional significance of the topographical aspects of the retino-cortical projection. In: R. Jung and H. Kornhuber (Eds.), *The Visual System: Neurophysiology and Psychophysics*, Berlin, Springer-Verlag, 1961, pp. 277-245.

Dunkerly, G.B. and Duncan, D., A light and electron microscopic study of the normal and degenerating corticospinal tract in the rat, *J. Comp. Neurol.*, 137 (1969) 155-184.

Ebner, F.F., Donoghue, J.P., Foster, R. and Christensen, B., The

organization of opossum somatic sensory-motor cortex, *Neurosci. Abstr.*, 2 (1976) 135.

Eisenman, L.M., Pontocerebellar projections to the paraflocculus in the rat, *Brain Res.*, 188 (1980) 550-554.

Eisenman, L.M., Pontocerebellar projections to the pyramis and copula pyramidis in the rat: evidence for a mediolateral topography, *J. Comp. Neurol.*, 199 (1981) 77-86.

Eisenman, L.M. and Noback, C.R., The ponto-cerebellar projection in the rat: differential projections to sublobules of the uvula, *Exp. Brain Res.*, 38 (1980) 11-17.

Elger, C.E., Speckmann, E.J., Caspers, H. and Janzen, R.W.C., Cortico-spinal connections in the rat. I. Monosynaptic and polysynaptic responses of cervical motoneurons to epicortical stimulation, *Exp. Brain Res.*, 28 (1977) 385-404.

Endo, K., Araki, T. and Yagi, N., The distribution and pattern of axon branching of pyramidal tract cells, *Brain Res.*, 57 (1973) 484-491.

Faull, R.L., The cerebellofugal projections in the brachium conjunctivum of the rat, *J. Comp. Neurol.*, 178 (1978) 519-536.

Finger, S., *Recovery From Brain Damage: Research and Theory*, New York, Plenum, 1978, pp. 115-134.

Fink, R.P. and Heimer, L., Two methods for selective silver impregnation of degenerating axons and their synaptic endings in the central nervous system, *Brain Res.*, 4 (1967) 369-374.

Finlay, B.L. and Cairns, S.J., Relationship of aberrant retinotectal projections to visual orienting after neonatal tectal damage in hamster, *Exp. Neurol.*, 72 (1981) 308-317.

Finlay, B.I., Wilson, K.G. and Schneider, G.E., Anomalous ipsilateral retinotectal projections in Syrian hamsters with early lesions: topography and functional capacity, *J. Comp. Neurol.*, 183 (1979) 721-740.

Flohr, H. and Precht, W., *Lesion-Induced Neuronal Plasticity in Sensorimotor Systems*, Springer-Verlag, New York, 1981.

Frost, D.O. and Schneider, G.E., Plasticity of retinofugal projections after partial lesions of the retina in newborn Syrian hamsters, *J. Comp. Neurol.*, 185 (1979) 517-568.

Fujito, Y., Tsukahara, N., Oda, Y., and Yoshida, M., Formation of functional synapses in the adult cat red nucleus from the cerebrum following cross-innervation of forelimb flexor and extensor

- nerves. II. Analysis of newly appeared synaptic potentials, *Exp. Brain Res.*, 45 (1982) 13-18.
- Goldberger, M., Locomotor recovery after unilateral hindlimb deafferentation in cats, *Brain Res.*, 123 (1977) 59-74.
- Goldberger, M.E., The role sprouting might play during the recovery of motor function. In: H. Flohr and W. Precht (Eds.), *Lesion Induced Neuronal Plasticity in Sensorimotor Systems*, Springer-Verlag, New York, 1981, 130-140.
- Goldberger, M.E. and Murray, M., Restitution of function and collateral sprouting in the cat spinal cord: the deafferented animal, *J. Comp. Neurol.*, 158 (1974) 37-54.
- Goldberger, M. and Murray, M., Recovery of movement and axonal sprouting may obey some of the same laws. In: Cotman, C.W. (Ed.), *Neuronal Plasticity*, New York, Raven Press, 1978, pp. 73-96.
- Goldman, P., An alternative to developmental plasticity: heterology of CNS structures in infants and adults. In: D.G. Stein, J.J. Rosen, and N. Butters (Eds.), *Plasticity and Recovery of Function in the Central Nervous System*, Academic Press, New York, 1974, 149-174.
- Goldman, P.S., Neuronal plasticity in primate telencephalon: anomalous projections induced by prenatal removal of frontal cortex, *Science*, 202 (1978) 768-770.
- Goldman, P. and Galkin, T., Prenatal removal of frontal association cortex in the fetal rhesus monkey: anatomical and functional consequences in postnatal life, *Brain Res.*, 152 (1978) 451-485.
- Goodman, D.C. and Horel, J., Sprouting of optic tract projections in the brain stem of the rat, *J. Comp. Neurol.*, 127 (1966) 71-88.
- Goodman, D.C., Jarrard, L.E. and Nelson, J.F., Corticospinal pathways and their sites of termination in the albino rat, *Anat. Rec.*, 154 (1966) 462.
- Gorska, T. and Sybirska, E., Effects of pyramidal lesions on forelimb movements in the cat, *Acta Neurobiol. Exp.*, 40 (1980) 843-859.
- Gorska, T., Woolsey, C.N. and Wetzels, A., Motor effects of cortical stimulation after chronic lesion on medullary pyramid in the dog, *Acta Neurobiol. Exp.*, 40 (1980) 861-879.
- Gorska, T. and Zalewska-Walkowska, M., Manipulatory forelimb movements in normal and pyramidotomized dogs, *Acta Neurobiol. Exp.*, 40 (1980) 964-984.

- Gramsbergen, A., Locomotion behavior after cerebellar lesions in the young rat, In: Flohr and W. Precht (Eds.), *Lesion-Induced Neuronal Plasticity in Sensorimotor Systems*, New York, Springer-Verlag, pp. 324-336, 1981.
- Gramsbergen, A. and Ijkema-Paassen, J., CNS plasticity after hemicerebellectomy in the young rat. Quantitative relations between aberrant and normal cerebello-rubral projections, *Neurosci. Letters*, 33 (1982) 129-134.
- Graybiel, A.M., Visuo-cerebellar and cerebello-visual connections involving the lateral geniculate nucleus, *Exp. Brain Res.*, 20 (1974) 303-306.
- Groos, W.P., Ewing, L.K., Carter, C.M. and Coulter, J.D., Organization of corticospinal neurons in the cat, *Brain Res.*, 143 (1978) 393-419.
- Hall, R.D. and Lindholm, E.P., Organization of motor and somatosensory neocortex in the albino rat, *Brain Res.*, 66 (1974) 23-38.
- Harlow, H.F., Blumquist, A.J., Thompson, C.I., Schiltz, K.A., and Harlow, M.K., Effects of induction-age and size of frontal lobe lesions on learning rhesus monkeys. In: R.L. Isaacson (Ed.), *The Neuropsychology of Development*, New York, Wiley, 1968, pp. 79-120.
- Harting, J.K. and Martin, G.F., Neocortical projections to the pons and medulla of the nine banded armadillo, *J. Comp. Neurol.*, 138 (1970) 483-500.
- Hayes, N.L. and Rustioni, A., Descending projections from brainstem and sensorimotor cortex to spinal enlargements in the cat, *Exp. Brain Res.*, 41 (1981) 89-107.
- Hicks, S.P. and D'Amato, C.J., Motor-sensory and visual behavior after hemispherectomy in newborn and mature rats, *Exp. Neurol.*, 29 (1970) 416-438.
- Hicks, S.P. and D'Amato, C.J., Motor-sensory cortex corticospinal system and developing locomotion and placing in rats, *Amer. J. of Anat.*, 143 (1975) 1-42.
- Hicks, S.P. and D'Amato, C.J., Locating corticospinal neurons by retrograde transport of horseradish peroxidase, *Exp. Neurol.*, 56 (1977) 410-420.
- Ho, D.P. and Leong, S.K., A cerebellar projection onto the pontine nuclei in the albino rat, *Exp. Brain Res.*, 30 (1977) 149-154.
- Hoddevik, G.H., The pontocerebellar projection to the paramedian

- lobule in the cat: an experimental study with the use of horseradish peroxidase as a tracer, *Brain Res.*, 95 (1975) 291-307.
- Hoddevik, G.H., The pontine projection to the flocculonodular lobe and the paraflocculus studied by means of retrograde axonal transport of horseradish peroxidase in the rabbit, *Exp. Brain Res.*, 30 (1977) 511-526.
- Horel, J., Phillips, C.G. and Porter, R., The effects of pyramidotomy on motor performance in the brush-tailed opossum (*Trichosurus vulpecula*), *Brain Res.*, 49 (1973) 181-184.
- Humphrey, T., The development of the pyramidal tracts in human fetuses, correlated with cortical differentiation, In: D.B. Tower and J.P. Schade (Eds.), *Structure and Function of the Cerebral Cortex*, Elsevier, Amsterdam, 1960, pp. 93-103.
- Isaacson, R.L., The myth of recovery from early brain damage. In: N.R. Ellis (Ed.), *Aberrant Development in Infancy*, Potomac, M., Erlbaum, 1975, pp. 1-25.
- Itoh, K., Efferent projections of the pretectum in the cat, *Exp. Brain Res.*, 30 (1977) 89-105.
- Jacobson, S., An electron microscope study of Wallerian degeneration in the pyramidal tract, *Neurol.*, 17 (1967) 298.
- Johnson, D.A. and Almlie, C.R., Age, brain damage, and performance. In: S. Finger (Ed.), *Recovery from Brain Damage: Research and Theory*, New York, Plenum, 1978, pp. 115-134.
- Jones, E.G. and Wise, S.P., Size, lamina and columnar distribution of efferent cells in the sensory-motor cortex of monkeys, *J. Comp. Neurol.*, 175 (1977) 391-438.
- Kalil, K. and Reh, T., Regrowth of severed axons in the neonatal central nervous system: establishment of normal connections, *Science*, 205 (1979) 1158-1161.
- Kalil, K. and Schneider, G.E., Motor performance following unilateral pyramidal tract lesions in the hamster, *Brain Res.*, 100 (1975) 170-174.
- Kartje-Tillotson, G., Neafsey, E.J. and Castro, A.J., Electrophysiological evidence for plasticity of corticospinal projections after neonatal cortical lesions in rats, *Anat. Rec.*, 202 (1982) 93.
- Kawaguchi, S., Yamamoto, T., Samejima, A., Itoh, K., and Mizuno, N., Morphological evidence for axonal sprouting of cerebellothalamic

- neurons in kittens after neonatal hemicerebellectomy, *Exp. Brain Res.*, 35 (1979a) 511-518.
- Kawaguchi, S., Yamamoto, T., Samejeima, A., Electrophysiological evidence for axonal sprouting of cerebellothalamic neurons in kittens after neonatal hemicerebellectomy, *Exp. Brain Res.*, 36 (1979b) 21-39.
- Kawamura, K., The pontine projection from the inferior colliculus in the cat. An experimental anatomical study, *Brain Res.*, 95 (1975) 309-322.
- Kawamura, K. and Chiba, M., Cortical neurons projecting to the pontine nuclei in the cat. An experimental study with the horseradish peroxidase technique, *Exp. Brain Res.* 35 (1979) 269-285.
- Kawamura, K. and Hashikawa, T., Studies of the tecto-ponto-cerebellar pathway in the cat by anterograde degeneration and axonal transport techniques, *J. Physiol. Soc. Jap.*, 37 (1975) 370-372.
- Kawamura, K. and Hashikawa, T., Projections from the pontine nuclei proper and reticular tegmental nuclei onto the cerebellar cortex in the cat. An autoradiographic study, *J. Comp. Neurol.* 201 (1981) 395-413.
- Kennard, M.A., Age and other factors in motor recovery from precentral lesions in monkeys, *Amer. J. Physiol.*, 115 (1936) 138-146.
- Kennard, M.A., Reorganization of motor function in the cerebral cortex of monkeys deprived of motor and premotor areas in infancy, *J. Neurophysiol.*, 1 (1938) 477-497.
- Kennard, M.A., Relation of age to motor impairment in man and subhuman primates, *Arch. Neurol. Psych.*, 44 (1940) 377-397.
- Kennard, M.A., Cortical reorganization of motor function: studies on a series of monkeys of various ages from infancy to maturity, *Arch. Neurol. Psych.*, 48 (1942) 227-240.
- King, J.S., Martin, G.F., and Biggert, T., The basilar pontine gray of the opossum. I. Morphology, *J. Comp. Neurol.*, 133 (1968) 439-446.
- Kolb, B. and Nonneman, A.J., Sparing of function with early prefrontal cortex lesions, *Brain Research*, 151 (1978) 135-148.
- Kosinski, R.J., Kartje-Tillotson, G. and Castro, A.J., Topographic analysis of dorsal column nuclear and motor cortical projections to the basilar pontine gray in rats, *Neurosci. Abstr.*, 8 (1982) 446.

- Kuypers, H.G.J.M., An anatomical analysis of cortico-bulbar connections to the pons and lower brain stem in the cat, *J. Anat. (Lond.)*, 92 (1958a) 198-218.
- Kuypers, H.G.J.M., Some projections from the peri-central cortex to the pons and lower brain stem in monkey and chimpanzee, *J. Comp. Neurol.*, 110 (1958b) 221-255.
- Kuypers, H.G.J.M., Cortico-bulbar connections to the pons and lower brain stem in man. An anatomical study, *Brain*, 81 (1958c) 364-388.
- Kuypers, H.G.J.M., Central cortical projections to motor and somatosensory cell groups, *Brain*, 83 (1960) 161-184.
- Kuypers, H.G.J.M., Corticospinal connections: postnatal development in the rhesus monkey, *Science*, 138 (1962) 678-680.
- Kuypers, H.G.J.M. and Brinkman, J. Precentral projections to different parts of the spinal intermediate zone in the rhesus monkey, *Brain Res.*, 24 (1970) 29-48.
- Kuypers, H.G.J.M., Anatomy of the descending pathways, In: J.M. Brookhart and V.B. Mountcastle (Eds.), *Handbook of Physiology-The Nervous System II*, Williams and Wilkins Co. Baltimore, 1981, pp. 597-666.
- Labar, D.R., Berman, N.E. and Murphy, E.H., Short and long term effects of neonatal and adult visual cortex lesions on the retinal projection to the pulvinar in cats, *J. Comp. Neurol.*, 197 (1981) 639-659.
- Laemle, L.K. and Labriola, A.R., Retinocollicular projections in the neonatal rat: An anatomical basis for plasticity, *Dev. Brain Res.*, 3 (1982) 317-322.
- Land, P.W. and Lund, R.D., Development of the rat's uncrossed retinotectal pathway and its relation to plasticity studies, *Science*, 205 (1979) 698-700.
- Laursen, A.M., A kinesthetic deficit after partial transection of a pyramidal tract in monkeys, *Brain Res.*, 31 (1971) 263-274.
- Lawrence, D.G. and Kuypers, H.G.J.M., The functional organization of the motor system in the monkey. I. The effects of bilateral pyramidal lesions, *Brain*, 91 (1968) 1-14.
- Lenneberg, E.H., The effects of age on the outcome of central nervous system disease in children, In: Isaacson, R.L. (Ed.), *The Neuropsychology of Development*, New York, Wiley, 1968, pp.

147-170.

- Lent, R. and Mendez-Otero, R., Plasticity of the ipsilateral retinotectal projection in early enucleated opossums: Changes in retinotopy and magnification factors, *Neurosci. Letters*, 18 (1980) 37-43.
- Leong, S.K., Effects of deafferenting cerebellar or cerebral inputs to the pontine and red nuclei in the albino rat, *Brain Res.*, 155 (1978) 357-361.
- Leong, S.K., A qualitative electron microscopic study of the corticopontine projections after neonatal cerebellar hemispherectomy, *Brain Res.*, 194 (1980) 299-310.
- Leong, S.K. and Lund, R.D., Anomalous bilateral corticofugal pathways in albino rats after neonatal lesions, *Brain Res.*, 62 (1973) 218-221.
- Leong, S.K., A qualitative electron microscopic investigation of the anomalous corticofugal projections following neonatal lesions in the albino rat, *Brain Res.*, 107 (1976a) 1-8.
- Leong, S.K., An experimental study of the corticofugal system following cerebral lesions in the albino rat, *Exp. Brain Res.*, 26 (1976b) 235-247.
- Leong, S.K., Sprouting of the corticopontine fibers after neonatal cerebellar lesion in the albino rat, *Brain Res.*, 123 (1977) 164-169.
- Lim, K.H., Leong, S.K., Aberrant bilateral projections from the dentate and interposed nuclei in albino rats after neonatal lesions, *Brain Res.*, 96 (1975) 306-309.
- Liu, C-N. and Chambers, W.W., Intraspinal sprouting of dorsal root axons, *Arch. Neurol. Psychiat.*, 79 (1958) 46-61.
- Liu, C-N. and Chambers, W.W., An experimental study of the corticospinal system in the monkey (*Macaca mulatta*). The spinal pathways and preterminal distribution of degenerating fibers following discrete lesions of the pre- and postcentral gyri and bulbar pyramid, *J. Comp. Neurol.*, 123 (1964) 257-284.
- Loesch, J. and Steward, O., Behavioral correlates of denervation and reinnervation of the hippocampal formation of the rat: recovery of alternation performance following unilateral entorhinal cortex lesions, *Brain Res. Bull.*, 2 (1977) 31-39.
- Lund, R.D., *Development and Plasticity of the Brain*, Oxford Univ.

Press, New York, 1978.

- Lund, R.D. and Lund, J.S., Reorganization of the retinotectal pathway in rats after neonatal and retinal lesions, *Exp. Neurol.*, 40 (1973) 377-390.
- Lund, R.D. and Webster, K.E., Thalamic afferents from the dorsal column nuclei; an experimental anatomical study in the rat, *J. Comp. Neurol.*, 130 (1967) 301-312.
- Martin, G.F., Efferent tectal pathways of the opossum (*Didelphis virginiana*), *J. Comp. Neurol.*, 135 (1969) 209-224.
- Martin, G.F., Cabana, T., Culberson, J.L., Curry, J.J. and Tschismadia, I., The early development of corticobulbar and corticospinal systems: studies using the North American Opossum, *Anat. Embryol.*, 161 (1980) 197-213.
- Martin, G.F. and King, J.S., The basilar pontine gray of the opossum (*Didelphis virginiana*). II. Experimental determination of neocortical input, *J. Comp. Neurol.*, 133 (1968) 447-462.
- Martin, G.F., Megirian, D. and Roebuck, A., Corticobulbar projections of the marsupial phalanei (*Trichosurus vulpecula*). I. Projections to the pons and medulla oblongata, *J. Comp. Neurol.*, 142 (1971) 275-295.
- McClung, J.R. and Castro, A.J., An ultrastructural study of ipsilateral corticospinal projections after frontal cortical lesions in newborn rats, *Anat. Rec.*, 181 (1975) 417-418.
- McCrea, R.A., Bishop, G.A. and Kitai, S.T., Morphological and electrophysiological characteristics of projection neurons in the nucleus interpositus of the cat cerebellum, *J. Comp. Neurol.*, 181 (1978) 397-420.
- Mihailoff, G.A., Principle neurons of the basilar pons as the source of a recurrent collateral system, *Brain Res. Bull.*, 3 (1978a) 319-332.
- Mihailoff, G.A., Anatomic evidence suggestive of dendrodendritic synapses in the opossum basilar pons, *Brain Res. Bull.*, 3 (1978b) 333-340.
- Mihailoff, G.A., Synaptogenesis in the rat basilar pontine nuclei, *Neurosci. Abstr.*, 8 (1982) 447.
- Mihailoff, G.A., Burne, R.A., Azizi, S.A., Norell, G. and Woodward, D.J., The pontocerebellar system in the rat: An HRP study. II. Hemispherical components, *J. Comp. Neurol.*, 197 (1981) 559-577.

- Mihailoff, G.A., Burne, R.A. and Woodward, D.J., Projections of the sensorimotor cortex to the basilar pontine nuclei in the rat: an autoradiographic study, *Brain Res.*, 145 (1978) 347-354.
- Mihailoff, G.A. and King, J.S., The basilar pontine gray of the opossum: a correlated light and electron microscopic analysis, *J. Comp. Neurol.*, 159 (1975) 521-552.
- Mihailoff, G.A. and Castro, A.J., Autoradiographic and electron microscopic degeneration evidence for axonal sprouting in the rat corticopontine system, *Neurosci. Lett.*, 21 (1981) 267-273.
- Mihailoff, G.A., Martin, G.F. and Linauts, M., The pontocerebellar system in the opossum, *Didelphis virginiana*, *Brain, Behav. Evol.*, 17 (1980) 179-208.
- Mihailoff, G.A. and McArdle, C.B., The cytoarchitecture, cytology, and synaptic organization of the basilar pontine nuclei in the rat. II. Electron microscopic studies, *J. Comp. Neurol.*, 195 (1981) 203-219.
- Mihailoff, G.A., McArdle, C.B. and Adams, C.E., The cytoarchitecture, cytology, and synaptic organization of the basilar pontine nuclei in the rat. I. Nissl and Golgi studies, *J. Comp. Neurol.*, 195 (1981) 181-201.
- Milner, B., Spraying of language functions after early unilateral brain damage. In: E. Eidelberg and D.G. Stein (Eds.), *Functional Recovery After Lesions of the Nervous System*, Neuroscience Research Program Bulletin, 12, 1974, 213-216.
- Mizuno, N., Mochizuki, K., Akimoto, C., Matsushima, R. and Sasaki, K., Projections from the parietal cortex to the brainstem nuclei in the cat, with special reference to the parietal cerebro-cerebellar system, *J. Comp. Neurol.*, 147 (1973) 511-522.
- Murakami, F., Katsumaru, H., Saito, K. and Tsukahara, N., A quantitative study of synaptic reorganization in red nucleus neurons after lesions of the nucleus interpositus of the cat: An electron microscopic study involving intracellular injection of horseradish peroxidase, *Brain Res.*, 242 (1982) 41-53.
- Murakami, F., Tsukahara, N. and Fujito, Y., Properties of the synaptic transmission of the newly formed corticorubral synapses after lesion of the nucleus interpositus of the cerebellum, *Exp. Brain Res.*, 30 (1977) 245-258.
- Murphey, E.H., Mize, R.R. and Schecter, P.B., Visual discrimination following infant and adult ablation of cortical areas 17, 18, and

- 19 in the cat, *Exp. Neurol.*, 49 (1975) 386-405.
- Mustari, M.J, and Lund, R.D., An aberrant crossed visual corticotectal pathway in albino rats, *Brain Res.*, 112 (1976) 37-44.
- Murray, E.A. and Coulter, J.D., Organization of corticospinal neurons in the monkey, *J. Comp. Neurol.*, 195 (1981) 339-365.
- Nah, S.H. and Leong, S.K., Bilateral corticofugal projections to the red nucleus after neonatal lesions in the albino rat, *Brain Res.*, 107 (1976a) 433-436.
- Nah, S.H. and Leong, S.K. An ultrastructural study of the anomalous corticorubral projection following neonatal lesions in the albino rat, *Brain Res.*, 111 (1976b) 162-166.
- Nah, S.H., Ong, L.S. and Leong, S.K., Is sprouting the result of a persistent neonatal connection?, *Neurosci. Lett.*, 19 (1980) 39-44.
- Nakamura, Y., Mizuno, N., Konishi, A. and Sato, M., Synaptic reorganization of the red nucleus after chronic deafferentation from cerebellorubral fibers: an electron microscopic study in the cat, *Brain Res.*, 82 (1974) 298-301.
- Neafsey, E.J. and Sievert, C., A second forelimb area exists in rat frontal cortex, *Brain Res.*, 232 (1982) 151-156.
- Neumann, S., Pritzel, M. and Huston, J.P., Plasticity of cortico-thalamic projections and functional recovery in the unilateral detelencephalized infant rat, *Behav. Brain Res.*, 4 (1982) 377-388.
- Nyberg-Hansen, R., Further studies on the origin of corticospinal fibers in the cat. An experimental study with the Nauta method, *Brain Res.*, 16 (1969) 39-54.
- Nyberg-Hansen, R. and Brodal, A., Sites of termination of corticospinal fibers in the cat. An experimental study with silver impregnation methods, *J. Comp. Neurol.*, 120 (1963) 369-391.
- Nyby, O. and Jansen, J., An experimental investigation of the corticopontine projection in *Macaca mulatta*, *Skr. Norske Vidensk.-Akad., I. Mat.-nat. Kl. No. 3* (1951) 1-47.
- Oka, H. and Jinnai, K., Common projection of the motor cortex to the caudate nucleus and the cerebellum, *Exp. Brain Res.*, 31 (1978) 31-42.
- Olszewski, J. Baxter, D. *Cytoarchitecture of the Human Brainstem*, J.B.

Lippincott Co., Philadelphia, 1954.

- Passingham, R., Perry, H., and Wilkinson, F., Failure to develop a precision grip in monkeys with unilateral neocortical lesions made in infancy, *Brain Res.*, 145 (1978) 410-414.
- Peterson, G.M. and Fracarol, L.A., The relative influence of the locus and mass of destruction upon the control of handedness by cerebral cortex, *J. Comp. Neurol.*, 68 (1938) 173-190.
- Petras, J.M. and Lehman, R.A.W., Corticospinal fibers in the racoon, *Brain Res.*, 3 (1966) 195-197.
- Peusner, K.D. and Morest, D.K., Neurogenesis in the nucleus vestibularis tangentialis of the chick embryo in the absence of the primary afferent fibers, *Neurosci.*, 2 (1977) 253-270.
- Phillips, C.G. and Porter, R., *Corticospinal Neurons: Their Role in Movement*, Academic Press, New York, 1977.
- Prendergast, J., Shusterman, R. and Phillips, T. Comparison of the effect of midthoracic spinal hemisection at birth or in adulthood on motor behavior in the adult rat, *Exp. Neurol.*, 78 (1982) 190-204.
- Price, A.W. and Fowler, S.C., Deficits in contralateral and ipsilateral forepaw motor control following unilateral motor cortical ablations in rats, *Brain Res.*, 205 (1981) 81-90.
- Pritzel, M. and Huston, J.P., Unilateral ablation of telencephalon induces appearance of contralateral cortical and subcortical projections to thalamic nuclei, *Behav. Brain Res.*, 3 (1981) 43-54.
- Raisman, G., Neuronal plasticity in the septal nuclei of the adult brain, *Brain Res.*, 14 (1969) 25-48.
- Raisman, G., What hope for repair of the brain?, *Annals of Neurol.*, 2 (1978) 101-106.
- Reh, T. and Kalil, K., Development of the pyramidal tract in the hamster. I. A light microscopic study, *J. Comp. Neurol.*, 200 (1981) 55-67.
- Reh, T. and Kalil, K., Development of the pyramidal tract in the hamster. II. An electron microscopic study, *J. Comp. Neurol.*, 205 (1982) 77-88.
- Rhoades, R.W., Expansion of the ipsilateral visual corticotectal projection in hamsters subjected to partial lesions of the visual cortex during infancy: Electrophysiological experiments, *J. Comp.*

- Neurol., 197 (1981) 447-458.
- Rhoades, R.W. and Chalupa, L.M., Functional and anatomical consequences of neonatal visual cortical damage in the superior colliculus of the golden hamster, *J. Neurophysiol.*, 41 (1978) 1466-1494.
- Ruegg, D.G., Seguin, J.J. and Wiesendanger, M., Effects of electrical stimulation of somatosensory and motor areas of the cerebral cortex on neurones of the pontine nuclei in squirrel monkeys, *Neurosci.*, 2 (1977) 923-927.
- Ruegg, D.G., Eldred, E. and Wiesendanger, M.W., Spinal projections to the dorsolateral nucleus of the caudal basilar pons in the cat, *J. Comp. Neurol.*, 179 (1978) 383-393.
- Sanides, D., Fries, W. and Albus, K., The corticopontine projection from the visual cortex of the cat: an autoradiographic investigation, *J. Comp. Neurol.* 179 (1978) 77-88.
- Scheff, S.W., Bernardo, L.S. and Cotman, C.W., Decline in reactive fiber growth in the dentate gyrus of aged rats compared to young rats following entorhinal cortex removal, *Brain Res.*, 199 (1980) 21-38.
- Schneider, G.E., Mechanisms of functional recovery following lesions of visual cortex or superior colliculus in neonate and adult hamsters, *Brain, Behav., and Evol.*, 3 (1970) 295-323.
- Schneider, G.E., Early lesions of superior colliculus: Factors affecting the formation of abnormal retinal projections, *Brain, Behav., Evol.*, 8 (1973) 73-109.
- Schneider, G.E., Is it really better to have your brain lesion early? A revision of the "Kennard Principle", *Neuropsychologia*, 17 (1979) 557-583.
- Schoen, J.H.R., Comparative aspects of the descending fibre systems in the spinal cord. In: J.C. Eccles and J.P. Schade (Eds.), *Progress in Brain Research: Organization of the Spinal Cord*, Elsevier, Amsterdam, 1964 Vol.11, pp. 203-222.
- Schreyer, D.J. and Jones, E.G., Growth and target finding by axons of the corticospinal tract in prenatal and postnatal rats, *Neurosci.*, 7 (1982) 1837-1853.
- Schroeder, D.M. and Jane, J.A., Projections of dorsal column nuclei and spinal cord to brainstem and thalamus in the tree shrew, *Tupaia glis*, *J. Comp. Neurol.*, 142 (1971) 309-350.

- Sharp, F.R. and Evans, K.L., Bilateral 2-deoxyglucose uptake by motor pathways after unilateral neonatal cortex lesions in the rat, *Dev. Brain Res.*, 6 (1983) 1-11.
- Shinoda, Y., Arnold, A.P. and Asanuma, H., Spinal branching of corticospinal axons in the cat, *Exp. Brain Res.*, 26 (1976) 215-234.
- Shinoda, Y., Zarzecki, P. and Asanuma, H., Spinal branching of pyramidal tract neurons in the monkey, *Exp. Brain Res.*, 34 (1979) 59-72.
- Shriver, J.E. and Noback, C.R., Cortical projections to the lower brain stem and spinal cord in the tree shrew (*Tupaia glis*), *J. Comp. Neurol.*, 130 (1967) 25-54.
- Sonnier, B.J., Villablanca, J.R., Olmstead, C., McAllister, J.P., and Gomez, F., Autoradiographic tracing of a crossed cortico-rubral pathway in cats with neonatal ablation of one cerebral hemisphere, *Neurosci. Abstr.* 8 (1982) 746.
- St. James-Roberts, I., A reinterpretation of hemispherectomy data without functional plasticity of the brain, *Brain and Language*, 13 (1981) 31-53.
- Stein, D.G., Rosen, J.J. and Butters, N., *Plasticity and Recovery of Function in the Central Nervous System*, Academic Press, New York, 1974.
- Steward, O., Reinnervation of dentate gyrus by homologous afferents following entorhinal cortical lesions in adult rats, *Science* 194 (1976) 426-428.
- Stewart, D.L. and Riesen, A.H., Adult versus infant brain damage: behavioral and electrophysiological effects of striatectomy in adult and neonatal rabbits. In: G. Newton and A.J. Riesen (Eds.), *Advances in Psychobiology*, Wiley, New York, 1972, 171-211.
- Sunderland, S., The projection of the cerebral cortex on the pons and cerebellum in the macaque monkey, *J. Anat. (Lond.)*, 74 (1940) 201-226.
- Swenson, R.S., Kosinski, R.J. and Castro, A.J., Analysis of caudal brainstem and spinal cord projections to the pontine gray in rats, *Neurosci. Abstr.*, 8 (1982) 446.
- Teuber, H.L., Mental retardation after early trauma to the brain. Some issues in search of facts. In: C.R. Angle and E.A. Berning (Eds.), *Physical Trauma as an Etiological Agent in Mental Retardation*, Bethesda, MD National Inst. Neurol. Dis. and Stroke,

1970, 7-28.

- Teuber, H.L., Recovery of function after brain injury in man. In: Outcome of Severe Damage to the Central Nervous System (Ciba Foundation Symposium), Elsevier, Amsterdam, 1975, 159-190.
- Teuber, H.L. and Rudel, R.G., Behavior after cerebral lesions in children and adults, *Dev. Med. Child Neurol.*, 4 (1962) 3-20.
- Tolbert, D.L., Marshall, C.A., Murphy, M.G., Collateral sprouting of somatosensory corticofugal axons into the cerebellar deafferented red nucleus, *Brain Res.*, 237 (1982) 473-478.
- Tower, S.S., Pyramidal lesion in the monkey, *Brain*, 63 (1940) 36-90.
- Tsang, Y.C., Maze learning in rats hemidecorticated in infancy, *J. Comp. Psych.*, 24 (1937) 221-254.
- Tsukahara, N., Synaptic plasticity in the mammalian central nervous system, *Neurosci.*, 4 (1981) 351-379.
- Tsukahara, N. and Fujito, Y., Physiological evidence of formation of new synapses from cerebrum in the red nucleus neurons following cross-union of forelimb nerves, *Brain Res.*, 106 (1976) 184-188.
- Tsukahara, N., Fujito, Y., Oda, Y., and Maeda, J., Formation of functional synapses in the adult cat red nucleus from the cerebrum following cross-innervation of forelimb flexor and extensor nerves. I. Appearance of new synaptic potentials, *Exp. Brain Res.*, 45 (1982) 1-12.
- Tsukahara, N., Hultborn, H., Murakami, F., and Fujito, Y., Electrophysiological study of formation of new synapses and collateral sprouting in red nucleus neurons after partial denervation, *J. Neurophysiol.*, 38 (1975) 1359-1372.
- Tsukahara, N. and Kosaka, K., The mode of cerebral excitation of red nucleus neurons, *Exp. Brain Res.* 5 (1968) 102-117.
- Tucker, T.J. and Kling, A., Differential effects of early and late lesions of frontal granular cortex in the monkey, *Brain Res.*, 5 (1967) 377-389.
- Tucker, T.J., Kling, A. and Scharlock, D.P., Sparing of photic frequency and brightness discrimination after striatectomy in neonatal cats, *J. Neurophys.*, 31 (1968) 818-832.
- Ullan, J. and Artieda, J., Somatotopy of the corticospinal neurons in the rat, *Neurosci. Letters*, 21 (1981) 13-18.

- Vahlsing, H.L. and Feringa, E.R., A ventral uncrossed corticospinal tract in the rat, *Exp. Neurol.*, 70 (1980) 282-287.
- Valverde, F., The pyramidal tract in rodents. A study of its relations with the posterior column nuclei, dorsolateral reticular formation of the medulla oblongata, and cervical spinal cord, *Zeit. Zell. Mikro. Anat.*, 71 (1966) 297-363.
- Wetzel, A.B., Thompson, V.E., Horel, J.A., and Meyer, P.M., Some consequences of perinatal lesions of the visual cortex in the cat, *Psychonomic Science*, 3 (1965) 381-382.
- Wiesendanger, R. and Wiesendanger, M., The corticopontine system in the rat. I. Mapping of corticopontine neurons, 208 (1982a) 215-226.
- Wiesendanger, R. and Wiesenganger, M., The corticopontine system in the rat. II. The projection pattern, *J. Comp. Neurol.*, 208 (1982b) 227-238.
- Wiesendanger, R., Wiesendanger, M. and Ruegg, D.G., An anatomical investigation of the corticopontine projection in the primate (*Macaca fascicularis* and *Saimiri scivreus*). II. The projection from frontal and parietal association areas, *Neurosci.*, 4 (1979) 747-765.
- Wirth, F.P., O'Leary, J.L., Smith, J.M. and Jenny, A.B., Monosynaptic corticospinal-motoneuron path in the racoon, *Brain Res.*, 77 (1974) 344-348.
- Wise, S.P. and Jones, E.G., Cells of origin and terminal distribution of descending projections of the rat somatic sensory cortex, *J. Comp. Neurol.*, 175 (1977) 129-158.
- Wise, S.P., Murray, E.A. and Coulter, J.D., Somatotopic organization of corticospinal and corticotrigeminal neurons in the rat, *Neurosci.*, 4 (1979) 65-78.
- Woolsey, C.N., Gorska, T., Wetzel, A., Erickson, T.C., Earls, F.J. and Allman, J.M., Complete unilateral section of the pyramidal tract at the medullary level in *Macaca mullatta*, *Brain Res.*, 40 (1972) 119-124.
- Yamamoto, T., Kawaguchi, S. and Samejima, A., Electrophysiological studies on plasticity of cerebellothalamic neurons in rats following neonatal hemicerebellectomy, *Jpn. J. Physiol.*, 31 (1981) 217-224.
- Yuen, H., Dom, R.M. and Martin, G.F., Cerebellopontine projections in the American opossum. A study of their origin, distribution, and

overlap with fibers from the cerebral cortex, J. Comp. Neurol.,
154 (1974) 257-286.

APPENDIX A

APPENDIX A - MEASUREMENT OF STIMULATION CURRENT

The micromapping technique employed in this dissertation utilized the following parameters: 350hz, 300msec train, and 0.25msec pulses. The depth of the electrode in the rat brain cortex was approximately 1.7mm. A diagram depicting the stimulation circuit is shown in Fig. 1. In this circuit the stimulus isolation unit (SIU) was used in order to obtain a constant current. The accurate measurement of stimulation current was obtained by utilizing the relationship of Ohm's law, or Voltage (V) = Current (I) x Resistance (R). Since we are using a known resistance (10,000 ohms), and reading the voltage directly from the oscilloscope screen, we can determine the value of the stimulus current. For example, if one division on the oscilloscope screen is equal to 0.1 volt, then $I = 0.1V \div 10,000\text{ohms} = 10\text{uamps}$.

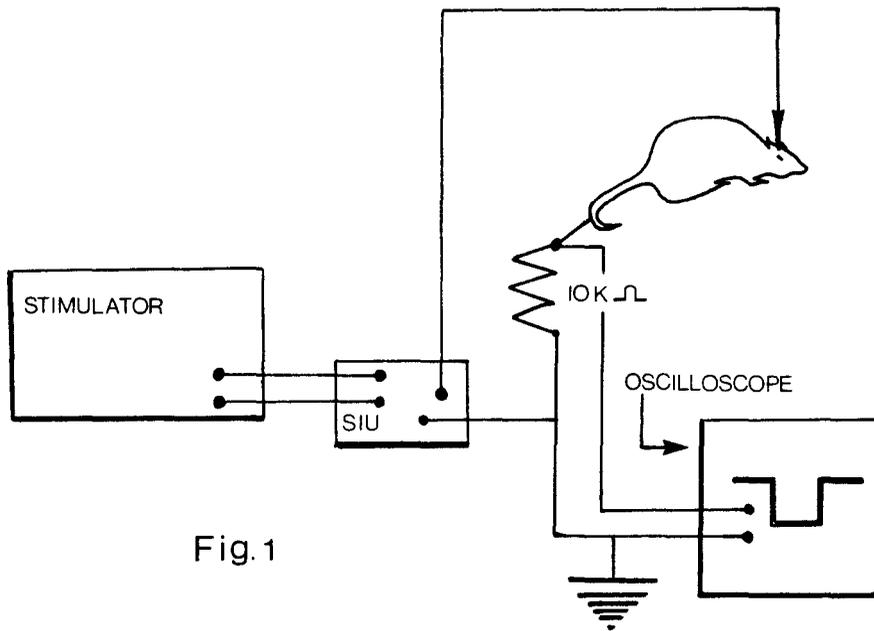


Fig.1

APPROVAL SHEET

The dissertation submitted by Gwendolyn Kartje-Tillotson has been read and approved by the following committee:

Dr. Anthony J. Castro, Director
Associate Professor, Anatomy, Loyola

Dr. E. J. Neafsey
Assistant Professor, Anatomy, Loyola

Dr. Faith W. LaVelle
Associate Professor, Anatomy, Loyola

Dr. Robert D. Wurster
Professor, Physiology, Loyola

Dr. Michael A. Collins
Professor, Biochemistry, Loyola

Dr. Gregory A. Mihailoff
Associate Professor, Cell Biology, University of Texas

The final copies have been examined by the director of the dissertation and the signature which appears below verifies the fact that any necessary changes have been incorporated and that the dissertation is now given final approval by the committee with reference to content and form.

The dissertation is therefore accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

December 5, 1983
Date

Anthony Castro
Director's Signature