1984

Analysis of Forelimb Motor Cortical Projections After Neonatal Hemicerebellectomy in Rats

Daniel L. O'Donoghue
Loyola University Chicago

ANALYSIS OF FORELIMB MOTOR CORTICAL PROJECTIONS AFTER NEONATAL HEMICEREBELLECTOMY IN RATS

BY

Daniel L. O'Donoghue

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

April

1984

DEDICATION

TO MY FAMILY

ACKNOWLEDGEMENTS

I would like to express my gratitude to Dr. Anthony J. Castro for his expert advice, his guidance and his time and efforts on my behalf. He gave me the opportunity 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. I would like to extend special thanks to Dr. E.J. Neafsey who willingly gave of his time to assist in my work.

I also thank the faculty members, graduate students and staff of the Department of Anatomy. Their support throughout my graduate career is greatly appreciated. In particular I thank Anna Zuk for her assistance in compiling this document; she has been a true friend.

The efforts of Dr. Gwendolyn Kartje-Tillotson require special recognition. Her assistance in many of the experiments was invaluable. Also, her editorial advice was most helpful.

To my wife, Eileen, I owe the largest debt of gratitude. Truly without her patience and support, this effort would not have been. In the same vein, I deeply appreciate our families for their contributions.

Lastly, thank you my Katie. While I cannot make up for the times I was not able to be with you, your love has always been precious to me. Now we can go "TO HIO!"

VITA

The author, Daniel L. O'Donoghue, was born on March 27, 1955 in Chicago, Illinois.

In the fall of 1973, after graduating from St. Ignatius College Prep., he entered Loras College, Dubuque, Iowa. He earned a Bachelor of Science degree in Biology in 1977. His graduate studies in the Department of Anatomy at Loyola University, Stritch School of Medicine, began in the summer of 1978. He held a Basic Science Research Fellowship while assisting in the teaching of gross anatomy, histology and neuroscience. In 1982 he became a member of the Society for Neuroscience. The following year he became a member of the American Association of Anatomists and was elected to the Society for Sigma Xi.

The author is married to Eileen M. O'Donoghue and they have one daughter, Kathryn.

In May, 1984, he will begin a postdoctoral fellowship in the Department of Anatomy at The Ohio State University under the supervision of Dr. James S. King.

TABLE OF CONTENTS

LIST OF FIGURES

Figures

GENERAL INTRODUCTION

The development of the motor cortex and cerebellum parallels both phylogenetically and ontogenetically the acquisition of complex motor movements (Allen and Tsukahara, 1974). In mammals, cortiocofugal and cerebellar connections develop primarily during the perinatal period (Altman and Sudarshan, 1975; Hicks and D'Amato, 1975; Lawrence and Hopkins, 1976; Donatelle, 1977; Altman, 1982; Schreyer and Jones, 1982). At this stage, neuronal projections appear more receptive to external influences as evidenced by numerous studies demonstrating the formation of anomalous projections in response to neonatal central nervous system (CNS) lesions (for reviews see, Cotman, 1978; Lund, 1978; Schneider, 1979, 1981; Tsukahara, 1981; Flohr and Precht, 1981; Finger and Stein, 1982). Although neuroanatomical remodelling (plasticity) is also observed after lesions in adult animals, it is commonly found to be more prominent after lesions in the newborn, suggesting that growing axons have a greater capacity to alter their distribution patterns than do more mature systems.

Behavioral tests of functional recovery after cerebellar injuries indicate that recovery is more complete after lesions in the young when compared to similar lesions placed in older animals and demonstrates that the cerebral cortex may participate in this recovery (Smith, et.al., 1974b). The role of the cerebral cortex in

compensating for neonatal cerebellar lesions is possibly related to the well documented neuroanatomical remodelling that results from such lesions (Lim and Leong, 1975; Leong 1977a,b; Castro, 1978; Kawaguchi and Yamamoto, 1981; Mihailoff and Castro, 1981; Tsukahara and Fugito, 1981; Castro and Mihailoff, 1982; Gramsbergen and Ijkma-Paassen, 1982).

The functional significance of such aberrant neuronal projections is not known, but they may be related to the less severe neurological dysfunctions after neonatal lesions in comparison to the deficits observed after similar lesions in older animals (Kennard, 1936, 1940, 1942; Stewart and Riesen, 1972; Milner, 1974; Teuber, 1975; Burgess, et al., 1982). This apparent correlation of recovery with plasticity suggests that anomalous pathways may contribute to recovery mechanisms. However, recent studies indicate that other factors besides age at time of lesion such as rehabilitation, nutrition, age at time of testing and even the function being tested may all result in different assessment of recovery (Bach-y-Rita, 1981; Finger and Stein, 1982). In addition, although some studies indicate that sparing of certain functions may be related to neuroanatomical remodelling, other studies imply that inappropriate projections result in maladaptive behavior (Goldman, 1974; Schneider, 1979; St. James-Roberts, 1981). Thus, the relative behavioral benefits of neuroanatomical remodelling are at present a subject of considerable debate. However, it does appear that recovery mechanisms are in part dependent upon the age of the animal at the time of lesion.

The experiments of this dissertation were designed to examine the cerebral motor cortical efferents after cerebellar lesions at various ages. Specifically, Experiment I used intracortical microstimulation techniques in animals that had sustained cerebellar lesions at different ages to determine the effect of these lesions on cortically-evoked forelimb movements. Initial studies indicated a significant difference in threshold current intensities needed to evoke ipsilateral forelimb movements after cerebellar lesions in the young. Experiment II examined, anatomically, motor cortical efferent projections to determine if aberrant neuronal projections might explain the anomalous responses observed in Experiment I. Experiment III was designed to determine the regions directly responsible for the transmission of cortically-evoked forelimb movements.

BACKGROUND

Electrical stimulation of the cerebral cortex may evoke body movements as initially described in pioneering studies on dogs by Fritch and Hitzig in 1870 as well as by Ferrier (1873) working on monkeys (for review see Dodds, 1878a,b). With the advancement of electrophysiological techniques, cortically-evoked movements were found to be most readily evoked by stimulation of the precentral region of the frontal cortex (for reviews see, Everts, 1981; and Asanuma, 1981). Further refinement demonstrated a precise somatotopic pattern within the frontal motor cortex of several species (Woolsey, 1958).

Motor Cortical Stimulation in the Rat

The motor areas of the rat lissencephalic cerebral cortex have been defined on the basis of electrophysiological techniques (Settlage, et al., 1949; Woolsey, 1958; Hall and Lindholm, 1974; Donoghue and Wise, 1982; Sanderson, et al., 1982; Donoghue and Parham, 1983; Sanderson, et al., 1984; Welker, et al., 1984). Initial studies concerning the somatotopy of the rodent motor cortex, as mapped by noting the body parts moved by epicortical stimulation, illustrated the whole body map with face and forelimb corresponding to large areas of cortex in comparison to small trunk and hindlimb representations (Settlage, 1949, Woolsey, 1958). Recent studies using more restrictive

microstimulation methods, have delineated the somatotopic motor cortical map. Different body parts were characterized by a patch-like somatotopic localization with a head area rostral to caudal limb and trunk areas (Hall and Lindholm, 1974; Neafsey and Sievert, 1982; Terreberry and Neafsey, 1982; Sanderson, et al., 1984).

Studies based on intracortical microstimulation techniques describe only contralateral movements (Hall and Lindholm, 1974; Sapienza, et al., 1981; Donoghue and Wise, 1982; Neafsey and Sievert, 1982; Sanderson, et al., 1984) although bilateral forelimb responses were observed using epicortical stimulation (Barron, 1934; Angel and Lemon, 1975; Elger, et al., 1977). While differences in the laterality of observed movements might reflect methodological differences, recording of spinal cord potentials after cortical stimulation in rats demonstrated both mono- and multisynaptic activation of ipsilateral as well as contralateral spinal motorneurons (Elger, et al., 1977). In agreement with these findings, a recent study of current intensity thresholds needed to evoke forelimb movements by intracortical microstimulation demonstrated bilateral movement responses (Kartje-Tillotson, et al., 1984); contralateral movements had considerably lower current thresholds than ipsilateral forelimb movements. Other studies involving motor cortical stimulation after medullary pyramidotomy in rats (Barron, 1934; Castro, et al., 1984), as well as monkeys (Woolsey, et al., 1972), dogs (Gorska, et al., 1980), and cats (Asanuma, et al., 1980) have demonstrated an elevation in

threshold current intensities needed to evoke contralateral limb movements. Although ipsilateral movement thresholds were generally not examined after pyramidotomy, the effect on contralateral movements corresponded to the predominantly crossed distribution of the corticospinal tract as classically described by numerous studies on several species (Heffner and Masterton, 1975; and for review see Armand, 1982). Presumably, the higher threshold currents corresponding to ipsilateral movements in normal animals (Kartje-Tillotson, et al., 1984) are mediated by multisynaptic relays through brainstem structures, spinal interneurons (Scheibel and Scheibel, 1966; Valverde, 1966) or by sparse monosynaptic ipsilateral corticospinal projections as indicated by electrophysiological studies (Elger, et al., 1977).

Anatomy of Motor Cortical Projections

The large pyramidal cells of layer V of motor and somatosensory cortex comprise the major source of descending cortical pathways in rats and other mammals (Hicks and D'Amato, 1977; Biendenback and Devito, 1980; Catsman-Berrevoets and Kuypers, 1981; Hayes and Rostioni, 1981; and for reviews see Kuypers, 1981; Armand, 1982). In early histological studies based on axonal degeneration after localized cortical lesions Sherrington (1889) described forelimb and hindlimb motor cortical projections to cervical and lumbar spinal cord levels, respectively. Recent anatomical studies using retrograde tracing techniques have confirmed this somatotopic distribution in rats (Wise,

et al., 1979; Ullan and Atrieda, 1981), cats (Coulter, et al., 1976; Groos, et al., 1978; Hayes and Rostioni, 1981) and monkeys (Coulter, et al, 1976; Jones and Wise 1977; Biber, et al., 1978).

In addition to spinal cord projections, cortical efferent fibers terminate in several brainstem areas including the red nucleus, pontine grey, and reticular formation, as well as the thalamus and striatum (Kuypers, 1981; Armand, 1982). Although some of these projections may represent collaterals of corticospinal fibers (Endo, et al., 1973; Catsman-Berrevoets and Kuypers, 1981), recent studies using retrograde labelling techniques (Wise and Jones, 1977; Catsman-Berrevoets and Kuypers, 1981) demonstrate that many corticorubral and corticoreticular fibers arise from neurons that are distinct from but intermingled with corticospinal neurons. This indicates that cortical stimulation, as used in motor cortical mapping studies, activates both types of neurons.

Concerning the laterality of cortical efferents, corticobulbar fibers primarily exert a contralateral effect by crossing or by projecting ipsilaterally to areas which in turn give origin to crossed projections. Similarly, the majority of corticospinal fibers decussate at lower medullary levels (Heffner and Masterton, 1975; Armand, 1982). In the rat, most fibers descend in the base of the contralateral dorsal funiculus (Valverde, 1966; Dunkerly and Duncan, 1969; Brown, 1971; Castro, 1975; Donatelle, 1977) although some fibers have been observed within the ipsilateral ventral funiculus (Valhsing and Ferringa, 1980).

Using degeneration techniques, Goodman and coworkers (1966) identified five corticospinal pathways and recent studies using more sensitive anterograde horseradish peroxidase tracing methods report similar findings (Sievert, personal communication).

Rodent corticospinal projections terminate primarily within the medial part of the spinal dorsal horn, i.e. lamina IV-VI (Brown, 1971; Castro, 1975; Donatelle, 1977; Wise and Jones, 1977). This distribution pattern, which is similar in distribution to somatosensory corticospinal fibers in cats (Nyberg-Hansen and Brodal, 1963) and monkeys (Coulter and Jones, 1977), suggests that the rodent corticospinal tract may primarily subserve a sensory function (Brown, 1971, 1974). However, direct corticospinal projections to the intermediate and ventral spinal gray, as observed in Golgi studies on rodents (Valverde, 1966), as well as electrophysiological demonstration of monosynaptic activation of spinal motor neurons (Elger, et al., 1977), indicates that the rodent corticospinal tract is indeed, in part, a motor pathway. The motor deficits observed after medullary pyramidotomy in rats (Castro, 1972) and hamsters (Kalih and Schneider, 1975) further support this conclusion.

Cerebro-Cerebellar Interrelations

Through well-described dense corticopontine projections, as well as several other pathways, the cerebral cortex can exert a strong influence on cerebellar activity. The cerebellum, in turn, can affect

cortical activity primarily through efferent projections which relay to the cortex via the thalamus. These pathways reflect an obvious close interrelationship between cerebral and cerebellar activity (Allen and Tsukahara, 1974; Wiesendanger, 1983) as further demonstrated by evoked potentials seen within the contralateral cerebellar hemisphere after cerebral-cortical stimulation (Allen and Tsukahara, 1974; Bower, et al., 1981). Additionally, stimulation of the cerebellar efferent fibers influence activity recorded in the contralateral motor cortex (Allen and Tsukahara, 1974; Asanuma and Hunsperger, 1975; Yamamoto, et al., 1979, Kawaguchi and Yamamoto, 1981; LiVolsi, et al., 1982). While the detailed significance of cerebro-cerebellar interactions are not understood, the cerebellum is generally considered to contribute to the planning and coordination of motor movements (for review see Brooks and Thach, 1981).

Of the massive number of cerebral efferent projections, only a small percentage continue to the spinal cord (Armand, 1982; Kuypers, 1981). In humans, an estimated 20 million fibers are found within the cerebral peduncle but only 500,000 continue as the corticospinal tract (Tomasch, 1969). Many of the remaining cortical projections terminate within precerebellar nuclei, especially in the basilar pontine nuclei (Bloedel and Courville, 1981). In the rat corticopontine fibers are primarily ipsilateral (Mihailoff, et al., 1978, 1981a; Mihailoff and Castro, 1981), and pontocerebellar fibers primarily relay to the contralateral hemisphere (Burne, et al., 1978; Mihailoff, et al.,

1981a,b). Similarly, rodent cortical efferent projections relay through the ipsilateral inferior olivary complex (Swenson and Castro, 1983) to the contralateral side of the cerebellum (Bloedel and Courville, 1981). Cortical relays through the precerebellar nuclei are topographically distributed to the cerebellar cortex such that somatosensory and associational cortices primarily influence the lateral cerebellar hemisphere while motor cortex influences the more medial, intermediate cerebellar cortex (Allen and Tsukahara, 1974; Eccles, 1977).

Cerebellar cortical efferent fibers, i.e. Purkinje cell axons to the deep cerebellar and vestibular nuclei, demonstrate a longitudinal zonation pattern with lateral hemispheral cortex projecting primarily to the dentate nucleus, vermal efferents to the fastigial and vestibular nuclei and intermediate areas to the interposed nuclei (Eccles, 1977; Corvaja and Pompeiano, 1979; Haines, et al., 1982). Pathways from these nuclei to areas involved in purposeful movements are primarily represented by dentato- and interposito- fugal fibers to the thalamic ventrolateral nucleus (Castro, 1978; Faull and Carman, 1978; Haroian, et al., 1981), as well as the red nucleus (Gwyn and Flumerfelt, 1974; Dekker, 1981; Gramsbergen and Ijkma-Paassen, 1982). The red nucleus gives rise to the crossed rubrospinal tract (Murray and Gurule, 1979; Huisman, et al., 1981, 1982, 1982), and the ventrolateral nucleus projects to the motor cortex (Jones and Leavitt, 1974; Donoghue, et al., 1979; Donoghue and Parham, 1983). The corticospinal

and rubrospinal tracts comprise the so-called lateral motor system concerned with the control of precise digital-limb movements (for review see Kuypers, 1981, 1982), and the density of cerebellar efferent projections directly to rubrospinal and indirectly to corticospinal neurons clearly underscores cerebellar involvement in precise motor control.

Plasticity After Neonatal Cerebellar Lesions In Rats

Sensorimotor corticopontine fibers are predominantly ipsilateral (for review see Brodal, 1982). However, after neonatal hemicerbellectomy, which causes considerable neuronal loss in the opposite pontine gray, corticopontine fibers that might have projected to the now atrophied pons show an anomalous increase of crossed projections to the intact contralateral pontine gray (Leong, 1977b, 1980; Mihailoff and Castro, 1981; Castro and Mihailoff, 1982). Accordingly, the spared cerebellar hemisphere can be influenced by both cerebral cortices, i.e., by the normal ipsilateral and the abnormal contralateral crossed corticopontine projections.

Cerebellar efferent projections may also remodel after cerebellar lesions. Normally, efferents traversing the superior cerebellar peduncle are predominantly crossed (Castro, 1978; Faull and Carman, 1978; Haroian, et al., 1981), but after hemicerebellectomy in newborn rats, a recrossing of projections to the ipsilateral red nucleus and ventrolateral thalamus was observed (Lim and Leong, 1975; Leong, 1977a;

Castro, 1978; Kawaguchi and Yamamoto, 1981; Tsukahara and Fujito, 1981; Gramsbergen and Ijkma-Paassen, 1982). These aberrant projections were similarly observed after hemicerebellectomy in kittens (Kawaguchi, et al., 1979b) where they were found to be electrophysiologically active (Kawaguchi, et al., 1979a; Tsukahara and Fujito, 1981; Yamamoto, et al., 1981).

Tracing the anomalous pathways observed after neonatal hemicerebellectomy indicates that corticopontine projections to the "wrong" pontine gray, which therefore in turn relay to the "wrong" cerebellar hemisphere, may be compensated by anomalous cerebellar efferent projections to the ipsilateral thalamus and red nucleus. Analysis of this circuitry suggests that two incorrectly lateralized pathways may result in a correctly lateralized cerebellar feedback to cortical and rubral motor pathways, thus raising the possibility that these aberrant pathways are functionally linked to recovery.

Several reports suggest that neuroanatomical plasticity may, in part, account for the functional recovery commonly observed after CNS lesions (Stein, et al., 1974; Cotman, 1978; Lund, 1978; Goldberger, 1980; Bach-y-Rita, 1981; Tsukahara, 1981; Finger and Stein, 1982). This possibility is often based on evidence that recovery of function, like plasticity, is typically more prominent after lesions in young animals as compared to lesions in mature animals (Johnson and Almli, 1978; Flohr and Precht, 1981; Finger and Stein, 1982). In reference to the deficits observed after cerebellar lesions, both clinical (Dow and

Moruzzi, 1958) and experimental (Smith, et al, 1974a,b) studies indicate less severe dysfunction when the injury occurs at a young age. However, studies of motor functions in rats sustaining cerebellar lesions from 5-30 days of age demonstrated better recovery in the animals receiving lesions at the older ages (Smith, et al., 1974b; Gramsbergen, 1981), although apparently all animals had less impairment in comparison to lesions in adult animals (Smith, et al., 1974a). The increasing deficits observed in animals sustaining lesions from 5-30 days of age contrasts with the decreasing anatomical plasticity observed after cerebellar lesions at various ages (Leong, 1977a). This inverse correlation has suggested that neuroanatomical plasticity may actually impede functional compensation (Gramsburgen, 1981), possibly because the anomalous pathways may disrupt the function of areas receiving abnormal inputs (Isaacson, 1975; Schneider, 1979, 1981).

Further study of the mechanisms of compensation demonstrated a reinstatement of cerebellar deficits after cerebral cortical lesions in adult rats that had recovered from hemicerebellectomy prior to weaning (Smith, et al.,1974b). The severity of the reinstated cerebellar symptoms was related to the age of the animals at the time of cerebellar lesion. Those sustaining hemicerebellectomy at 10 or 15 days of age were more adversely affected by the secondary cortical lesion than were animals with cerebellar lesions at 21 days.

The apparent participation of the cerebral cortex in compensation for cerebellar lesions in young rats has been speculatively

attributed to neuroanatomical plasticity (Smith, et al., 1974b). In view of this possibility, a preliminary study examined limb movements evoked by intracortical microstimulation in adult rats that sustained hemicerebellectomy at two days of age in order to detect possible changes in motor cortical functions (O'Donoghue, et al., 1983). In comparison to control animals, ipsilateral forelimb movements were elicited in these at significantly lowered current intensities in comparison to control animals. This observation formed the basis for the experiments presented in this dissertation.

A Study of Forelimb Movements Evoked by Intracortical Microstimulation After Hemicerebellectomy in Newborn, Young or Adult Rats

ABSTRACT

In normal adult rats microstimulation of the cerebral motor cortex evokes low threshold contralateral and higher threshold ipsilateral forelimb movements. In all groups contralateral forelimb movements were elicited at threshold currents of 7-11 uamps; these values are equivalant to threshold values found in unoperated controls. Also, animals with cerebellar lesions at 45 or 120 days of age showed ipsilateral forelimb movements at the same mean threshold values (45 uamps) as unoperated control animals. However, the mean ipsilateral thresholds for adult animals sustaining hemicerebellar lesions at 2, 10 or 21 days of age were significantly lower (22, 16 and 22 uamps, respectively) in comparison to values found in controls and in animals with lesions placed at older ages. These data demonstrate that hemicerebellectomy at preweaning ages, but not afterwards, will induce alterations in the electrophysiologic properties of the rat cerebral motor cortex and thereby support previous studies which suggest cortical involvement in compensation for neonatal cerebellar lesions.

INTRODUCTION

Neurological dysfunctions after central nervous system (CNS) lesions in the newborn are often less severe than those observed after similar lesions in older animals (Kennard, 1936, 1940, 1942; Steward and Riesen, 1972; Milner, 1974; Teuber, 1975; Burgess, et.al., 1982; and for review see Johnson and Almli, 1978). Several authors (Schneider, 1970; Goldberger, 1981; Gramsbergen, 1981) suggest that neuroanatomical plasticity, i.e., the formation of anomalous pathways after CNS damage, may provide the basis for the observed functional recovery. This possibility is supported by numerous observations that plasticity, like recovery, is more prominent after lesions in the newborn (Lund, 1978; Schneider, 1981; Tsukahara, 1981; Finger and Stein, 1982). However, it is also possible that anomalous projections may actually disrupt the normal functions of areas receiving abnormal inputs and therefore hinder recovery (Schneider, 1979). Indeed, several reports indicate that behavioral recovery is more impaired by lesions in the newborn than in the adult (Goldman, 1974; Gramsbergen, 1981; Schneider, 1981; Kolb and Holmes, 1983; and for review see Isaacson, 1975; Schneider, 1979). Although these apparently conflicting reports concerning recovery in relation to age may reflect differences in the locus and extent of CNS damage, as well as varying methods of assessing behavior (Finger and Stein, 1982), it nonetheless

seems evident that the degree of recovery may differ according to the age of the animal at the time of lesion.

Considering the effects of cerebellar lesion, both clinical (Dow and Moruzzi, 1958) and experimental studies (Smith, et al. 1974a,b) indicate that recovery may be more prominent after lesions in the young. Additionally, cerebral cortical lesions in adult rats that had previously sustained a cerebellar lesion imposed greater deficits in comparison to animals receiving only cortical lesions (Smith, et al., 1974b). The severity of deficits observed after secondary cortical lesions increased the younger the animal at the time of the cerebellar ablation.

To further examine cortical involvement in recovery mechanisms, the present study was designed to examine limb movements evoked by microstimulation of the cerebral cortex in adult rats that had sustained neonatal hemicerebelletomy. Previous work demonstrates that cortically-evoked limb movements can provide a useful model for studying motor cortical plasticity (Kartje-Tillotson, et al., 1984). In view of initial findings demonstrating ipsilateral forelimb movements which were evoked at abnormally low current intensities (O'Donoghue, 1983), the present study examines in detail these responses in animals that sustained cerebellar lesions at various ages.

MATERIALS AND METHODS

Forty-two male, Long-Evans, black-hooded rats were used in this study. At 2, 10, 21, 45 or 120 days of age, 6-8 animals per age-group sustained right hemicerebellar lesions. An additional three animals received right occipital cortical lesions at two days of age and seven normal adult animals served as non-lesion controls. Intracortical microstimulation was initiated 3-6 months postoperatively. Upon completion of stimulation procedures, animals were sacrificed by anesthetic overdose and vascular perfusion with 10% buffered formalin. The brains were removed, photographed, and inspected for the extent of cerebellar or cortical lesions.

Lesion Procedures

Animals receiving cerebellar or occipital cortical lesions at 2 days of age were anesthetized by hypothermia; all remaining animals sustained lesions while under sodium pentabarbitol anesthesia (40 mg/kg). After removal of the right half of the occiput, the cerebellum was bisected mid-sagitally with a number 11 scalpel blade. The right side of the cerebellum was then aspirated through a small glass pipette; the bleeding was controlled with gelfoam, and the skin was sutured. Occipital lesions were similarly made by aspiration with glass pipettes. After recovering from the anesthesia, pups were returned to their mothers until weaning.

Cortical Stimulation Procedures

Intracortical microstimulation procedures were the same as those employed in previous studies in this laboratory (Kartje-Tillotson, et al., 1984). Animals were anesthetized with ketamine hydrochloride (100mg/kg, I.M.). The hair on their forelimbs was clipped to facilitate the observation of evoked movements. Rectal temperature was servo-controlled to maintain body temperature at 36-38 C. With the animal secured in a stereotaxic frame and the forelimbs pendant, the skin over the skull was incised and retracted and the cisterna magna was drained to prevent cortical swelling. Next, the bone over the left frontal cortex was removed; the dura was left intact and moistened with warm saline to protect the cortex. A glass insulated tungsten wire electrode (Neafsey, 1981) with a 125 um exposed tip was used to deliver 0.25 msec negative pulses at 350 hz in 300 msec trains at a depth of 1.7 mm in the left frontal cortical region. With bregma as a point of reference, multiple electrode penetrations were made in 0.25-0.50 mm increments in both caudal to rostral and medial to lateral directions. The current intensities varied from 5 to 100 uamps and were monitored by an oscilloscope as the voltage drop across a 10,000 ohm resistor. In nine animals taken from groups sustaining cerebellar lesions at 2, 10, or 21 days of age, both cerebral cortices were mapped in an alternating fashion; in all other animals, only the left cerebral cortex was mapped.

At each penetration which elicited a contralateral forelimb

movement at the initial stimulus current of 30 amps, the current intensity was slowly decreased until no contralateral response occurred. The threshold current was recorded as the lowest current that consistently elicited an observed movement. After the current threshold for the contralateral forelimb movement was determined, the current intensity was gradually increased until either a movement was evoked in the forelimb ipsilateral to the stimulating electrode or a current of 100 uamps was reached. The threshold current for this response was then determined. At least ten electrode penetrations where stimulation evoked movements in both forelimbs were mapped in each animal.

In an effort to minimize subjective bias, two investigators collaborated in the determination of threshold currents. One investigator with no knowledge of the current intensity applied or the age group of the animal would determine if a response was elicited while the other investigator controlled the current intensities without examining the response. The evoked movements were characterized according to the type of movement, and the location of all electrode penetrations were plotted on scaled drawings of the cerebral hemisphere with the boney landmark bregma as the point of reference.

Data Analysis

Statistical analyses of threshold values were performed on stimulation points selected according to two criteria: (1) no movements of other body parts could be elicited below the threshold current for

the contralateral forelimb response, and (2) the threshold for the contralateral response had to be below 30 uamps and the ipsilateral below 100 uamps. Ten penetrations meeting these two criteria were mapped in each animal; an analysis of variance and a comparison of the least squared values were used to determine the significance of differences between the mean threshold current values for the different groups.

RESULTS

Some variation in the extent of cerebellar ablations was found, particularly among animals sustaining lesions at 2 days of age (fig 1). However, all lesions included the right cerebellar cortex, white matter and nuclei. The largest lesions involved most of the vermis and the smallest lesion spared the entire vermis. In all animals the medullary white matter between the spared left hemisphere and the right side of the caudal brain stem was completely severed (fig. 2a, b).

Non-Lesion Control Animals

In non-lesion control animals, contralateral forelimb responses were observed at current intensities with a mean threshold value of 10 uamps (fig. 3a). At threshold current intensities, these movements were typically of small amplitude across a single joint. Elbow flexion or wrist extension were most common, and shoulder and digit movements were evoked less often. However, digit movements were commonly found within the rostral forelimb area of the motor cortex. As current intensities were increased above threshold levels, the contralateral response invariably increased in range and vigor involving movements across several joints. Ipsilateral forelimb movements were evoked at threshold currents with a mean value of 38 uamps (fig. 3a). These movements were similar to contralateral responses as far as the types of movments observed and the joints acted upon. However, in addition

to higher threshold values, ipsilateral responses typically showed no significant increase in amplitude with above-threshold currents intensities. A variety of combinations of contra- and ipsilateral forelimb movements were seen at the points studied. For example, at some points both limbs might demonstrate extension or flexion movements, or one extension and the other a flexion. Although the particular joints involved in the bilaterally evoked movements had no consistent regularity, wrist and elbow movements were most common.

Cerebellar Lesion-Groups

The mean threshold current intensities that evoked contralateral forelimb movements upon stimulation of the left cortex in all lesion groups were similar to the values found in adult control animals (fig. 3a). However, adult rats that sustained right hemicerebellectomy at 2, 10, or 21 days of age exhibited ipsilateral forelimb movements at threshold levels that were significantly ($p<0.005$) lower in comparison to both non-lesion control animals and to animals that sustained cerebellar lesions at 45 or 120 days of age. In comparison to our non-lesion control animals as well as to previous studies (Hall and Lindholm, 1975; Neafsey and Sievert, 1982), the basic cortical somatotopic patterns and the types of evoked forelimb movements did not appear altered by cerebellar lesions at any of the ages studied (fig 4).

Microstimulation of both cerebral hemispheres in nine adult rats that had received hemicerebellar ablations at pre-weaning ages showed

that low-threshold ipsilateral forelimb movements could be evoked from either cortex (fig. 3b). The threshold current values that evoked movements were similar for both cortices.

Occipital Cortical Lesion-Group

To control for the effects of neonatal surgical procedures, the left cortex of mature rats that had received right occipital cortical lesion at 2 days of age (fig. 5) was mapped in the same manner as cerebellar ablated animals. Stimulation currents needed to elicit both contralateral and ipsilateral forelimb movements from the left motor cortex were similar to the values found for normal control animals (fig. 6).

DISCUSSION

Intracortical microstimulation in adult rats evoked bilateral forelimb movements. In animals that had sustained hemicerebellar lesions prior to weaning, ipsilateral movements were evoked at significantly lower threshold current intensities in comparison to those needed to elicit similar movements after cerebellar lesions at older ages or in normal control animals (fig. 3a). These low-threshold ipsilateral forelimb responses seen after neonatal hemicerebellectomy could be evoked upon stimulation of either cerebral hemisphere (fig. 3b). Although threshold current values were affected, the normal somatotopy of the rat motor cortex, as previously described (Hall and Lindholm, 1975; Neafsey and Sievert, 1982) did not appear to be altered by any of the cerebellar lesions. Neonatal occipital cortical lesions did not induce abnormally low ipsilateral threshold current values (fig. 6), implying that the lowered thresholds are not a "non-specific" reaction to neonatal brain injury.

The observed decrease in threshold currents needed to evoke ipsilateral forelimb movements corresponds to previous behavioral studies indicating cerebral cortical involvement in recovery from deficits induced by cerebellar lesions (Smith, et al., 1974a). Also, Smith and coworkers (1974a,b) found that the degree of both functional recovery and cortical involvement in compensation for cerebellar damage

declines when cerebellar lesions are incurred at older ages. Our findings of a decrease in current intensities needed to elicit ipsilateral forelimb movements from the frontal cortex after cerebellar lesions in the young, but not mature animals may provide electrophysiological support for these behavioral observations.

The anatomical basis for the threshold responses observed in the present study is not understood. However, the elevation of current thresholds needed to evoke contralateral limb movements after a medullary pyramidotomy in normal monkeys (Woolsey, et al., 1972), dogs (Gorska, et al., 1980), cats (Nieoullin and Gahery, 1978; Asanuma, et al., 1981), and rats (Barron, 1933; see also Expt. III), demonstrates the involvement of corticospinal fibers in the mediation of low-threshold movements (for review see Asanuma, 1981). The rodent corticospinal tract is predominantly a crossed pathway (King, 1910; Dunkerley and Duncan, 1969; Brown, 1971) with a small ipsilateral component (Goodman et al. 1966; Vahlsing and Feringa, 1980). In normal rats the higher threshold currents needed to evoke ipsilateral movements, in comparison to threshold currents for contralateral responses, may reflect the paucity of ipsilateral corticospinal fibers.

Recent studies using intracortical microstimulation of the spared cortex of adult rats that sustained unilateral neonatal cortical lesions also demonstrated low-threshold ipsilateral forelimb movements (Nation, et al., 1983; Kartje-Tillotson, et al., 1984). These movements apparently correspond to the anomalous ipsilateral

corticospinal tract which develops in response to neonatal cortical lesions (Hicks and D'Amato, 1970; Leong and Lund, 1973; Castro, 1975). Whether a similar anomalous corticospinal tract develops after neonatal cerebellar lesions has not been determined (Expt. II).

Studies of plasticity after neonatal hemicerebellectomy have revealed the formation of anomalous corticopontine (Leong, 1977b, 1980; Castro and Mihailoff, 1982) and cerebellofugal projections (Lim and Leong, 1975; Leong, 1977a; Castro, 1978; Kawaguchi and Yamamoto, 1981; Gramsbergen and Ijkma-Paasson, 1982). While these aberrant projections may, in part, account for our findings, cerebellofugal remodelling does not occur after cerebellar lesions in 15 day old rats (Leong, 1977a). We observed low-threshold ipsilateral forelimb movements in animals with lesions at 21 days of age. It thus appears unlikely that the reported anomalous corticopontine and cerebellofugal pathways mediate these responses. However, the participation of the spared cerebellar hemisphere could be tested by examining cortically evoked movements after total cerebellectomy (Expt. III).

Figure 1. Camera lucida drawing showing the variation in the extents of lesions plotted from all animals used in this study. The solid area represents the smallest cerebellar lesion and the solid plus the hatched area represents the largest lesion.

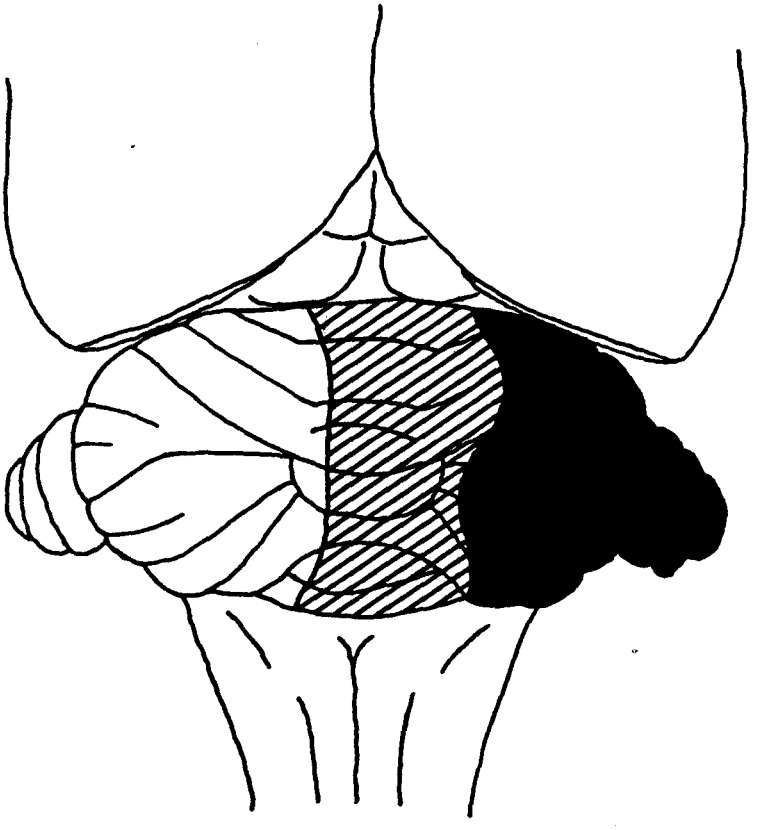
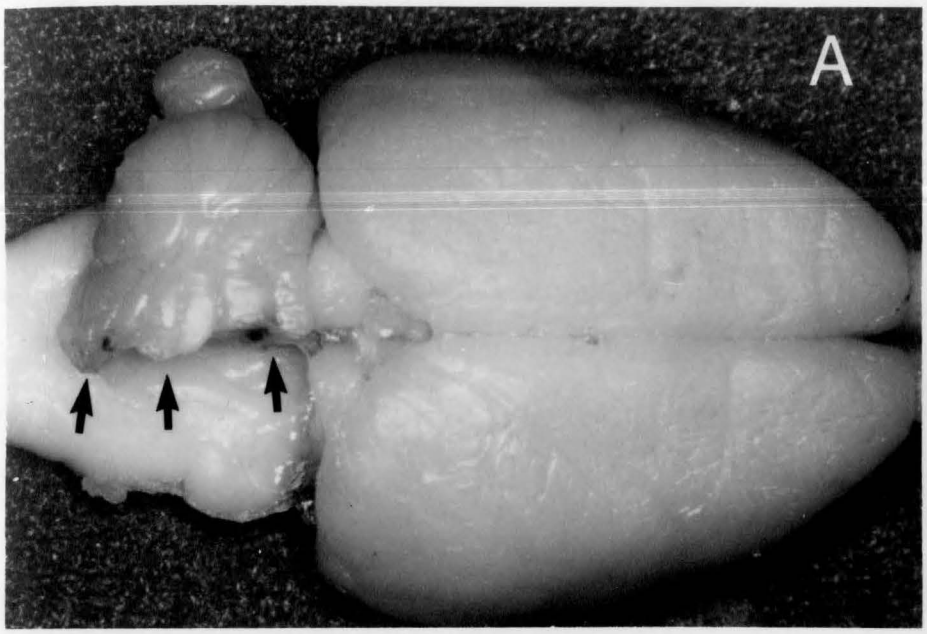


Figure 2. Cerebellar Lesions

A. Dorsal view of the brain of an adult animal that sustained hemicerebellectomy at 2 days of age.

B. Transverse section through the metenecephalon of an animal after neonatal hemicerebellectomy. Arrows in both figures indicate the edges of the cerebellar tissue spared by the neonatal lesion.


A

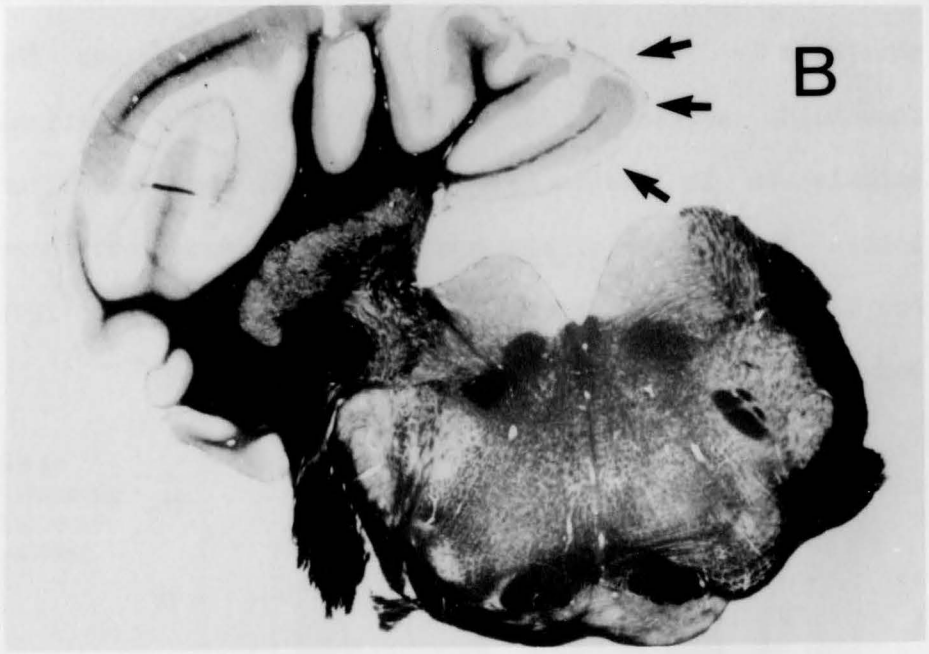
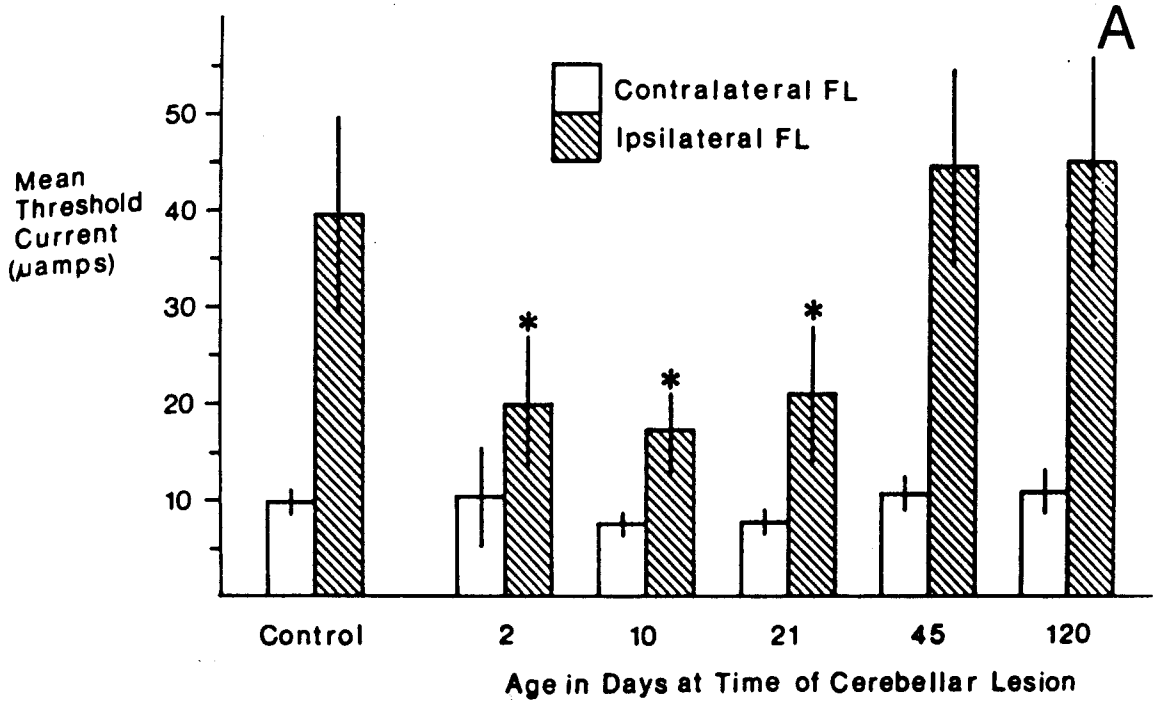

B

Figure 3. Histogram of the threshold current values for forelimb movements. Contralateral = open column; ipsilateral = hatched column.

A. The mean threshold current values (bar = 1 S.D.) in uamps that evoked forelimb movements by left motor cortical stimulation in animals that had sustained cerebellar lesions at the different ages studied. * indicates significant difference from controls ($P<0.005$).

B. The mean threshold current values (bar = 1 S.D.) in uamps that evoked contra- and ipsilateral forelimb movements by right cortical stimulation. Values for threshold currents found after left motor cortical stimulation in adults sustaining right hemicerebellar lesion at 2 days of age are shown for comparison. Note the similarities in threshold currents between the left and right hemispheres.


A
Contralateral FL
Ipsilateral FL
Mean Threshold Current (μamps)
50
40
30
20
10
*
*
*
Control
2
10
21
45
120
Age in Days at Time of Cerebellar Lesion

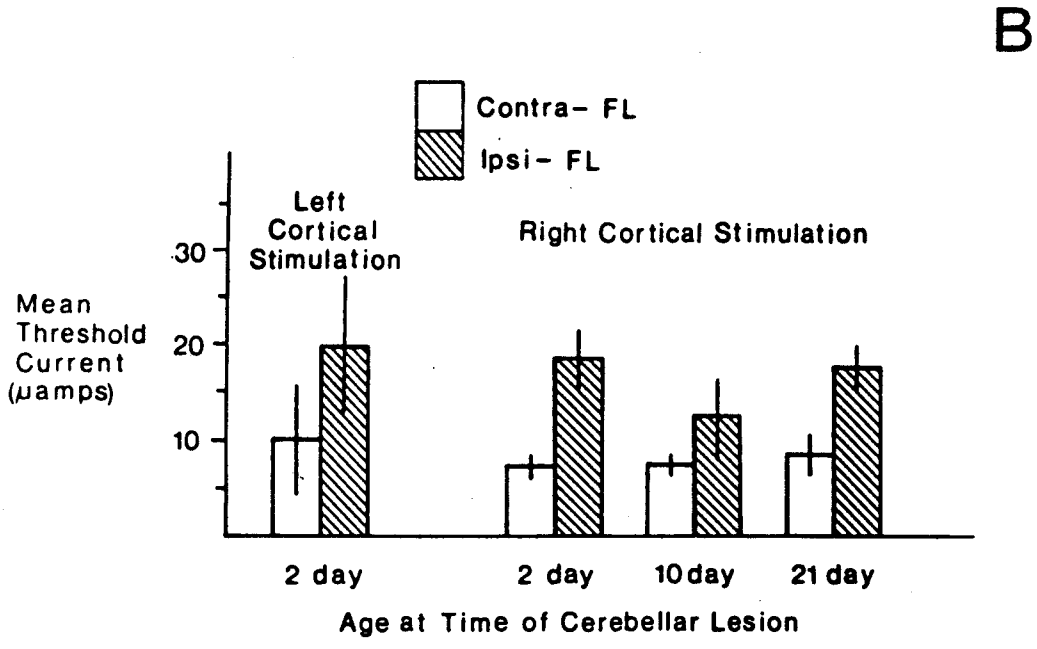

B
Contra- FL
Ipsi- FL
Left Cortical Stimulation
Right Cortical Stimulation
Mean Threshold Current (μamps)
30
20
10
2 day
2 day
10 day
21 day
Age at Time of Cerebellar Lesion

Figure 4.

A. Diagramatic representation of the cerebral cortical frontal poles. On the left cortical surface, all electrode penetrations mapped in one adult non-lesion control animal are illustrated. * represents the location of the penetrations where bilateral forelimb responses were evoked. Statistical analysis was performed on the data from these penetrations. Penetrations that were not used for analyses are shown as the type of movement evoked. B = bregma; Df = digit flexion; Ef = elbow flexion; HL = hindlimb; N = neck, nr = no response; To = tongue; V = vibrissae; We = wrist extension. The somatotopy of the normal rat cerebral cortex is illustrated on the right hemisphere (results obtained by Neafsey and Sievert, 1982; with the authors' permission). Dots represent electrode penetrations; FL = forelimb.

B. Drawing of the dorsal surface of the rat brain showing the location of electrode penetrations corresponding to the left hemisphere illustrated in fig. A.

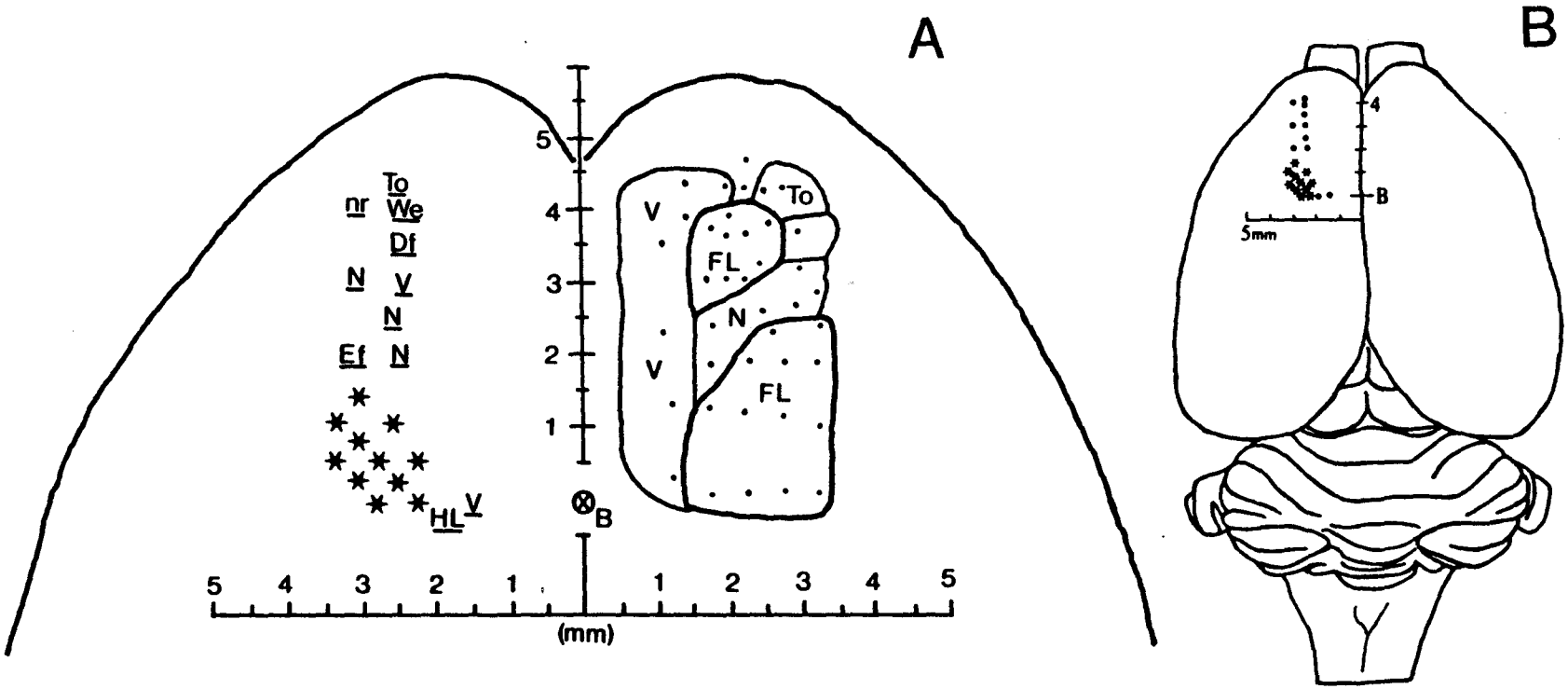

A
B
nr
To
We
Df
N
V
N
Ef
N
HL
V
To
V
FL
N
V
FL
⊗B
5
4
3
2
1
1
2
3
4
5
(mm)
4
B
5mm

Figure 5. Photograph of an adult rat brain that sustained a neonatal right occipital cortical lesion (arrows).

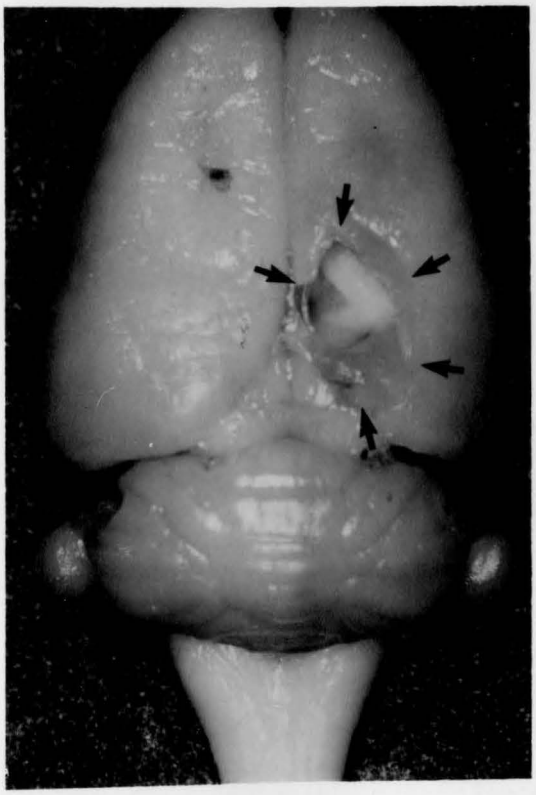


Figure 6. Histogram of mean threshold current values (bar = 1 S.D.) for forelimb responses evoked by stimulation of the left intact cortex of the adult rats after neonatal right occipital cortical lesion. The threshold current values for non-lesion control animals are included for comparison.

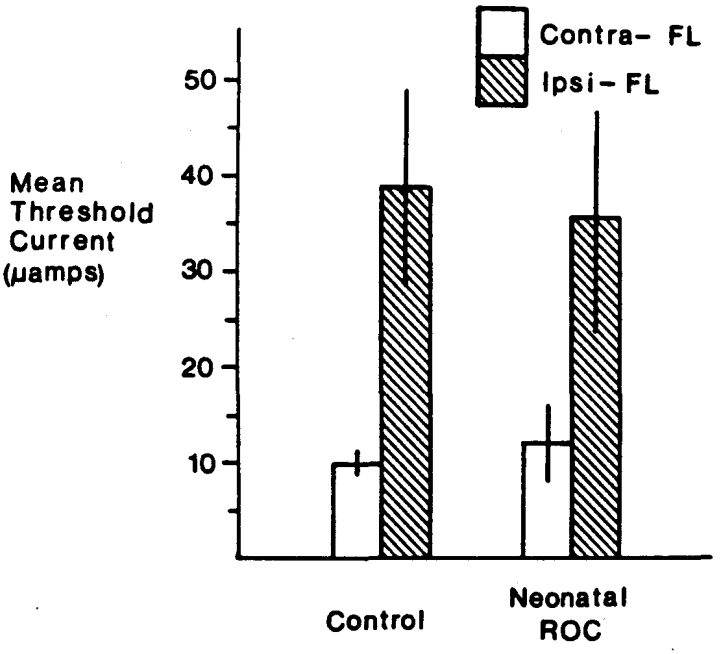
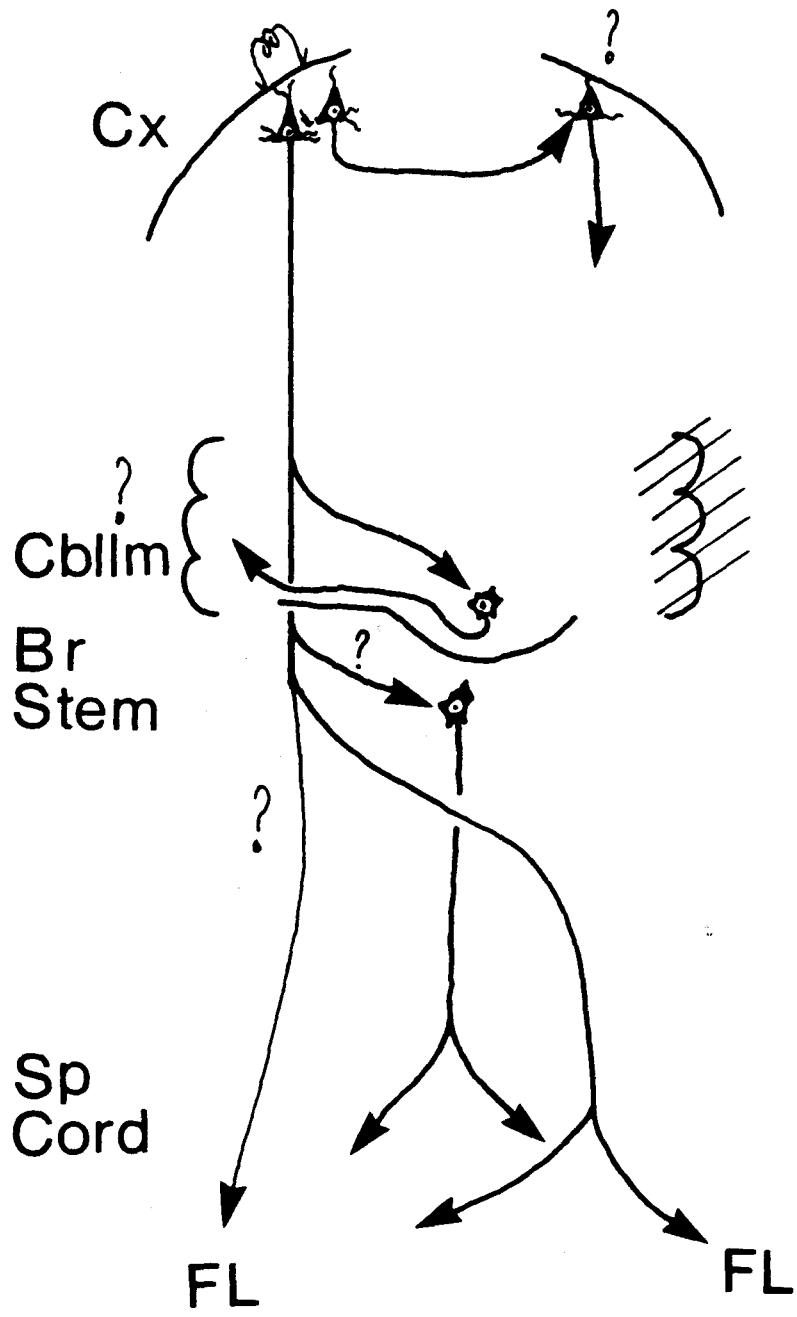

Contra- FL
Ipsi- FL
Mean
Threshold
Current
(μamps)
50
40
30
20
10
Control
Neonatal
ROC

Figure 7. Summary diagram demonstrating various possible pathways (arrows) for the mediation of abnormal, low-threshold, ipsilateral forelimb movements (FL) found upon intracortical microstimulation in adult rats after neonatal hemicerebellectomy (indicated by hatched area): Cx = cortex; Cbllm = cerebellum;Br stem = brain stem; Sp Cord = spinal cord.


Cx
?
?
Cbllm
Br
Stem
?
?
Sp
Cord
FL
FL

An Anatomical Study Using Anterograde Transport of WGA/HRP

ABSTRACT

The neuroanatomical basis for abnormally low-threshold ipsilateral forelimb responses evoked from the motor cortex after neonatal hemicerebellectomy is unknown. Therefore the present study was undertaken to examine the possibility that neonatal cerebellar lesions induce aberrent cortical efferent projections that might mediate low-threshold responses. Injections of WGA/HRP were made into low-threshold forelimb cortical areas and the distribution of cortical efferent projections was traced to the brainstem and spinal cord. No neuroanatomical remodelling was found in either direct corticospinal projections or corticobulbar projections to cell groups that might influence the ipsilateral spinal cord. Therefore, no pathway that might obviously mediate abnormal, low-threshold, cortically-evoked ipsilateral forelimb movements was determined.

INTRODUCTION

After cerebellar lesions, functional recovery as measured by motor testing is more prominent in young rats as compared to the recovery observed after similar lesions in older animals (Smith, et al., 1974a, b). Cerebral cortical involvement in this compensation is suggested by studies of the effects of cortical lesions in mature rats which had previously sustained cerebellar lesions neonatally. The deficits resulting from secondary cortical lesions were more severe in comparison to the effects of similar lesions placed in control animals or in animals sustaining cerebellar lesions beyond the neonatal period (Smith, et al. 1974a,b). In accordance with these behavioral data motor cortical stimulation in adult rats that had sustained a hemicerebellar lesion prior to weaning, evoked ipsilateral forelimb movements at abnormally low current intensities (Expt. I). These low-threshold movements were not found in normal animals or in rats that received cerebellar lesions after weaning.

In search of the neuroanatomical basis for the abnormal low-threshold, ipsilateral forelimb movements, the present study was undertaken to examine possible alterations in motor cortical projections which may develop after neonatal hemicerebellectomy. Previous studies involving neonatal cortical rather than cerebellar lesions also demonstrated low threshold ipsilateral forelimb movements

evoked by intracortical microstimulation (Nation, et al., 1983; Kartje-Tillotson, et al., 1984). These movements apparently correspond to aberrant ipsilateral corticospinal fibers observed after such lesions (Hicks and D'Amoto, 1970; Leong and Lund, 1973; Castro, 1975), but whether corticospinal remodelling similarly occurs after neonatal hemicerebellectomy has not been previously examined.

MATERIALS AND METHODS

Motor cortical efferent projections were examined in adult Long-Evans, black-hooded, rats that had sustained hemicerebellectomy at 2 days of age (n=10) and in non-lesion control adult animals (n=6). Axonal projections were demonstrated according to histological procedures based on the orthograde transport of pressure injected wheat germ agglutin/horseradish peroxidase (WGA/HRP)(Mesulam, 1982).

Surgical Procedures

Cerebellar lesions were made on pups anesthetized by hypothermia. The bone over the cerebellum was removed and the dura reflected. Visualized through a dissecting microscope, the cerebellum was divided mid-sagitally with a number 11 scalpel blade and the right half of the cerebellum was aspirated using a small glass pipette. After wound closure, the pups were warmed by an incandescent light and returned to their mothers until weaning. At 4-6 months postoperatively and also using non-lesion controls, intracortical microstimulation methods (as described in Expt. I) were used to identify the position of forelimb motor cortex. Since some inter-animal variation exists, several loci were stimulated to determine the exact location of forelimb areas responsive to low-threshold current (<15 uamps) stimulation (fig. 1 and 4).

Multiple injections (4-10) of 1% WCA/HRP in saline (w/v) were made into low-threshold forelimb cortical areas. At each injection site, 0.02 ul was delivered at 1.1 mm depth through a drawn pipette (25um tip) fitted to a 1 ul Hamilton syringe. At 2-4 days post-injection, animals were sacrificed by anesthetic overdose with sodium pentobarbitol and vascular perfusion with saline followed for 30-40 minutes by a gluteraldehyde/paraformaldehyde (1.25/1.0%) in phosphate buffer (pH, 7.4) fixative. A 10% sucrose phosphate buffer flush was perfused for 30-40 minutes after fixation.

Histology

After perfusion, the brains and spinal cords were removed and stored in 10% sucrose in phosphate buffer. Drawings of the cerebellar lesions were made using a stereoscopic dissecting microscope with a camera lucida attachment. Serial frozen sections, cut at 40 um on a sliding microtome, were collected into phosphate buffer and processed for HRP with tetramethyl benzidine (TMB) as the chromogen according to the methods outlined by Mesulam (1982). Sections were mounted out of acetate buffer (3.3 pH) at 4 degrees C on to chrom-alum/gelatin coated slides. Two sets of slides consisting of alternate sequential sections were made so that half the sections could be stained with 1% pyronin Y. Using a camera lucida, the outlines and landmarks of the Nissl stained sections were drawn. The distribution of HRP-labelled axons and cell bodies on adjacent unstained sections, as observed by polarized light

(Illing and Wastle, 1979), was plotted onto the outline drawings.

RESULTS

In normal animals, forelimb motor cortical projections distributed primarily to areas within the ipsilateral mesencephalon, pontine nuclei, inferior olive, and contralaterally to the caudal medullary reticular formation and to the contralateral side of the cervical spinal cord. Considerably fewer fibers were observed to the pontine reticular formation and trigeminal complex, as well as to the ipsilateral side of the spinal cord. After neonatal hemicerebellectomy, anomalous cortical projections were observed to the mesencephalon and contralateral basilar pontine nuclei; no remodelling of corticospinal fibers was found.

Cortical Injection Sites

Cortical injection sites were centered in areas which elicited forelimb movements at low-threshold current (<15uamps) intensities (fig 1). As observed histologically, the reaction product surrounded the electrode tracts (fig. 2), and although reacted with the sensitive chromogen TMB, the majority of injection sites appeared to be restricted to the agranular lateral (i.e. motor) cortex (Donoghue and Wise, 1982). Three large injections areas in one control and two in experimental animals encroached upon the granular (i.e. somatosensory) cortex both caudally and laterally.

Thalamic Labelling

The pattern of retrogradely labelled cells within the thalamus was defined to further delineate the effective area of uptake and transport of the WGA/HRP. In general agreement with previous studies of thalamic projections to the motor cortex in rodents (Donoghue and Parham, 1983), retrogradely labelled cells were found in several diencephalic nuclei (figs. 3A-D and 7A) including the ventral medial, ventral lateral, posterior complex, central lateral, central medial, parafascicular, and also in zona incerta. Labelled cells were also found only in the most ventral and medial portions of the ventrobasal complex. Because corticothalamic fibers were observed predominantly to those regions that contained retrogradely labelled cells, the precise details of distribution patterns were made difficult to ascertain, but no evidence of anterograde labelling to the lateral edges of the ventrobasal complex was found indicating no spread of HRP from the injection site into the primary sensory cortex. No difference in thalamic labelling was observed after neonatal hemicerebellectomy (fig. 5A-E).

Forelimb Motor Cortical Efferent Projections in Normal Rats

Callosal projections crossed the midline in the corpus callosum and extended from the level of bregma to about 1.5 mm anterior to bregma. The area of anterograde labelling in the frontal cortex

contralateral to the injection was similar in extent and position to the injection site (Figs. 1C and 2B). Retrogradely labelled soma were seen mostly in the superficial cortical layers within areas demonstrating anterograde labelling. As previously described (Cospito and Kultas-Ilinsky, 1981), motor corticostriate projections distributed bilaterally to the lateral aspect of the rostral caudate-putamen (not illustrated).

The distribution of motor cortical projection as found after a small injection site (figs. 1,2A) is illustrated in fig. 3. Descending from the injection site, labelled fibers formed compact bundles that traversed the ipsilateral caudate-putamen and then converged into the medial aspect of the cerebral peduncle in the rostral mesencephalon. Many labelled fibers coursed through the substantia nigra (fig. 3C) and distributed densely to the ipsilateral pretectal region, ventrolateral to the superior colliculus (figs. 3E-G and 7B). A lighter band of labelling extended from the anterior pretectal nucleus through the reticular formation and into the lateral portion of the periaqueductal gray. Other labelled fibers rimmed the ventral aspect of the red nucleus and extended dorsomedially toward the nucleus Darkschewitsch. Although a few fibers were found throughout the red nucleus, the most prominent label was primarily found rostromedially. Within the mesensephalic tegmentum, the few fibers that appeared to emerge from the peduncle coursed dorsolaterally toward the anterior pretectal nucleus. In those animals receiving larger cortical injections, all

projections were more evident and an additional sparse labelling across the deep layers of the superior colliculus was observed. Although a few fibers were found to the medial parabrachial nucleus within the caudal midbrain tegmentum (fig. 3K), no label was found in the inferior colliculus.

As the peduncle descended into the pons, a dense projection to the ipsilateral rostral third of the pontine gray formed two longitudinal columns (fig. 3I). One column was located ventral to the peduncle and the other more ventrolateral. These columns did not extend beyond the rostral pontine gray. At mid to lower pontine nuclear levels, another area of dense ipsilateral corticopontine label formed three columns (fig. 3J) localized medially, ventrally and ventrolaterally (fig. 7C). Also, a small projection to the ipsilateral dorsal peduncular nucleus was found. Crossed corticopontine projections were observed only at mid to lower pontine levels and only to the most medial pontine gray (fig. 3J). The most caudal sections through the pontine nuclei showed no labelling (fig. 3K). At the pontomedullary junction the pyramidal tract coursed through the fibers of the trapezoid body. At this level a few labelled fibers projected into the medial pontine reticular formation (fig. 3L-O).

In the medulla, descending fibers continued within the pyramid with no apparent localization (fig. 3O-U). Cortico-olivary projections (fig. 3R-T) emerged dorsally from the pyramid and distributed throughout the rostral-caudal extent of the medial portion of the

ipsilateral dorsal accessory olive. Labelled fibers were also located in the rostral portion of the dorsal lamella and lateral bend of the principle olive as well as within the caudal part of the medial accessory olive. No contralateral cortico-olivary fibers were found. Emerging dorsally from the medullary pyramid, a few fibers distributed bilaterally to the medullary reticular formation (fig. 3O-S) and to the rostral area of the nucleus solitarius (fig. 3Q). Continuing caudally, the majority of fibers within the pyramid decussated at the spinomedullary junction (fig. 8A), coursed dorsally to an area just ventral to the nucleus cuneatus and then turned caudally to enter the base of the dorsal funiculus of the spinal cord (fig. 3V-X). Many fibers left the decussating bundle and distributed to the contralateral medullary reticular formation at that level. A small recurrent bundle branched rostrally from the pyramidal decussation, rimmed the ventral surface of the nucleus cuneatus and ascended to the rostral medulla (fig. 3V-R). Fibers leaving this bundle projected to the dorsolateral reticular formation, the spinal trigeminal nucleus pars interpolaris and to the rostral and ventral portions of the nucleus cuneatus. In animals with larger cortical injections more labelling was found in these nuclei in addition to labelling within the trigeminal nucleus pars caudalis and the nucleus gracilis. Although the preponderance of labelled fibers decussated, a few fibers veered from the decussation and coursed to the ipsilateral nucleus cuneatus where some ascended or descended similar to the contralateral projection (fig. 3W,X). A few

fibers did not enter the decussation and thus descended directly into the ipsilateral ventral funiculus of the spinal cord.

In cervical segments of the spinal cord labelled fibers distributed heavily to the contralateral intermediate and ventral gray matter with fewer projections to the dorsal horn (figs. 6 and 8C). Lighter labelling was also observed within the ipsilateral intermediate to ventral gray matter. In a few animals, thoracic segments were processed and the distribution of labelled fibers to these levels was sparse in comparison to cervical segments.

Motor Cortical Projections After Neonatal Hemicerebellectomy

Although the extent of cerebellar lesions varied, all lesions included the cerebellar cortex, white matter and deep nuclei on the right side (fig. 5M-P). The largest lesions included the entire vermis while the smallest spared the vermis. In all animals there was a complete separation of the remaining part of the cerebellum from the right side of the brainstem. Hemicerebellectomy caused a marked atrophy within brainstem precerebellar nuclei. Contralatateral to the lesion, the pontine gray demonstrated a substantial loss in area (fig. 5I-K) and the inferior olivary complex appeared entirely absent (fig. 5R-V). Ipsilaterally, the external cuneate and the lateral reticular nuclei could not be identified.

The corticobulbar projections in these animals differed slightly from those seen in normal rats. Although difficult to quantify,

corticorubral projections appeared slightly increased throughout the ipsilateral red nucleus, but like controls no contralateral corticorubral fibers were found (fig. 5F-H). However, projections to the contralateral nucleus Darkschewitsch were apparently more dense than normal (fig. 5E-F). While there were dense terminations to rostral and caudal levels of the atrophied pons, an increase in crossed corticopontine projections to the contralateral medial and ventral pontine gray was observed (fig. 7D). Although the inferior olivary complex ipsilateral to the injected cortex (contralateral to the hemicerebellar lesion) was absent, no crossed cortico-olivary fibers were found. Cortical projections to the bulbar reticular formation appeared similar to those found in normal adults (fig. 8B).

No corticospinal remodelling was observed. As in control animals, corticospinal projections were predominantly to the contralateral intermediate and ventral gray matter of the spinal cord with no increase in the sparse ipsilateral corticospinal projections (fig. 8D). Even after large injections, the pattern of corticospinal projections resembled those found after a large injection in the cortex of a normal rat.

DISCUSSION

Previous studies of forelimb movements evoked by cortical stimulation in animals that sustained medullary pyramidotomy indicated that contralateral low-threshold movements are mediated by the predominately crossed corticospinal tract (Barron, 1934; Woolsey, 1972; Asanuma, et al., 1980; Gorska, et al., 1980; Castro, et al., 1984). The present study was initiated to determine whether corticospinal remodelling, in the form of anomalous ipsilateral fibers, might occur after neonatal hemicerebellectomy and thus explain the abnormal low-threshold ipsilateral movements observed after such lesions (Expt. I). However, no corticospinal plasticity was observed.

In view of the lack of CST remodelling, an alternative explanation for the mediation of low-threshold ipsilateral forelimb movements might have involved motor cortical relays through brainstem areas. However, substantial forelimb motor cortical projections to areas such as the red nucleus or the reticular formation which might relay to the ipsilateral side of the spinal cord, were not found. The observed increase in crossed corticopontine projections, in agreement with previous reports (Leong, 1977b; Mihailoff and Castro, 1981; Castro and Mihailoff, 1982), as well as the marginal increase in projections to midbrain areas, i.e., the red nucleus and the nucleus Darkschewitsch, do not seem to provide a plausible explanation for

ipsilateral forelimb movements. The possibility of corticopontine remodelling contributing to low-threshold forelimb movements by relays through the spared cerebellar hemisphere could be tested by examining the effects of total cerebellectomy on cortically evoked movements (Expt. III). The additional possibility that motor cortical stimulation excites callosal connections to the opposite motor cortex which thereby might elicit movements ipsilateral to the stimulating electrode could be tested by disrupting these connections by callosotomy or by cortical lesions (Expt. III).

Projections from forelimb motor cortex as defined by intracortical microstimulation have not been previously reported in the rat. The observed corticospinal projections to the intermediate and ventral gray areas of the cervical spinal cord, although less dense, agree with previous studies using similar methods on monkeys (Coulter and Jones, 1977). In contrast, earlier reports using less sensitive anatomical techniques on rats described corticospinal terminations primarily within the dorsal gray areas of the spinal cord (Brown, 1971; Castro, 1975; Donatelle, 1977; Wise and Jones, 1977). While the majority of fibers coursed contralaterally in the base of the dorsal funniculus, in agreement with numerous reports (Heffner and Masterton, 1975; Armand, 1982), a small ipsilateral bundle within the ventral funiculus was also found in our animals. In addition to previous anatomical studies (Valhsing and Ferringa, 1980), ipsilateral CST fibers have also been indicated by electrophysiological studies demonstrating monosynaptic

activation of cervical motoneurons (Elger, et al., 1977). While these ipsilateral CST fibers might contribute to ipsilateral cortically-evoked movements, no quantitative increase of these fibers was observed in correlation with the decrease in current thresholds for ipsilateral movements after neonatal cerebellar lesions.

The distribution of corticobulbar fibers agrees in general with previous reports for rats (Torvik, 1956; Valverde, 1962; Zimmerman, et al., 1964; Wise and Jones, 1977), as well as for other species (Martin, et al., 1974; Nakamura, et al., 1983; see Kuypers, 1981 for review). However, our findings typically showed more precisely localized termination patterns in some regions, i.e. the pontine gray. These more restricted patterns reflect the placement of small injections within the stimulation defined motor cortex whereas previous studies employed less sensitive anterograde tracing techniques such as degeneration staining after cortical lesions (Torvik, 1956; Valverde, 1962; Zimmerman, et al., 1964).

Corticobulbar projections may be involved in the transmission of cortically-evoked responses. Previous studies have demonstrated that movements can be evoked from the motor cortex even after medullary pyramidotomy (Barron, 1933; Woolsey, et.al., 1972; Nieoullin and Gahery, 1978; Gorska, et.al., 1980; Asanuma, et.al., 1981). Corticobulbar projections to the red nucleus and reticular formation apparently mediate these "non-pyramidal" responses. However, the threshold currents for responses mediated through the non-pyramidal

system are higher than thresholds via the pyramidal (corticospinal) tract (Asanuma, et.al., 1981). Although the neuroanatomical substrates for high threshold responses are not precisely known, these thresholds are related to the diffusely organized extrapyramidal system.

Reticulospinal neurons, which project mono- and multisynaptically to alpha motorneurons (Shapovalov, 1972), receive projections from the cerebral cortex (Peterson, et al., 1974). However, further electrophysiological studies demonstrated that there is a convergence of several different afferent systems upon these same neurons (Peterson, et al., 1974) and that these reticulospinal neurons have collaterals to multiple levels of the spinal cord (Peterson, et al., 1974, 1975). Accordingly, the precise movements commonly observed after cortical stimulation are not likely to be mediated via the reticulospinal pathways.

Anatomical studies using double retrograde tracing techniques have further verified the branchings of not only reticulospinal but also rubrospinal projection fibers (Martin, et al., 1979, 1983; Huisman, et al., 1981, 1982, 1983). In addition, non-pyramidal responses are related to proximal limb musculature both electrophysiologically (Asanuma, et al, 1981) and functionally (Kuypers, 1982). In the present study, corticobulbar projections to areas that might relay cortically-evoked responses to the spinal cord were sparse and no difference was found between non-lesion animals and neonatal operates. Even if an anamolous projection to the reticular

formation had occurred, this system lacks the specificity needed to mediate low-threshold responses. Therefore, abnormal low threshold ipsilateral forelimb responses are probably not mediated via corticobulbar projections.

List of Abbreviations:

BC - brachium conjunctivum

BP - brachium pontis

CC - crus cerebrum

Cc - central canal

Ce - external cuneate nucleus

Fm - facial motor nucleus

FR - fasciculus retroflexus

Ic - inferior colliculus

ICP- inferior cerebellar peduncle

IOC- inferior olivary complex

LC - locus coeruleus

Lc - nucleus linearis

Mg - medial geniculate

ML - medial lemniscus

Mt - motor trigeminal

Nc - nucleus cuneatus

Nd - dentate nucleus

NDk- nucleus Darkschewitsch

Nf - fastigial nucleus

Ng - nucleus gracilis

Ni - nucleus interpositus

Nr - red nucleus

Nrl- lateral reticular nucleus

Nts- nucleus solitarius

Pag- periaqueductal gray

PC - posterior commissure

Pf - parafascicular nucleus

Pg - pontine gray

Po - posterior complex

Pr - pretectum

Py - pyramid

Sc - superior colliculus

Sn - substantia nigra

St - spinal trigeminal nucleus

Vb - ventrobasal complex

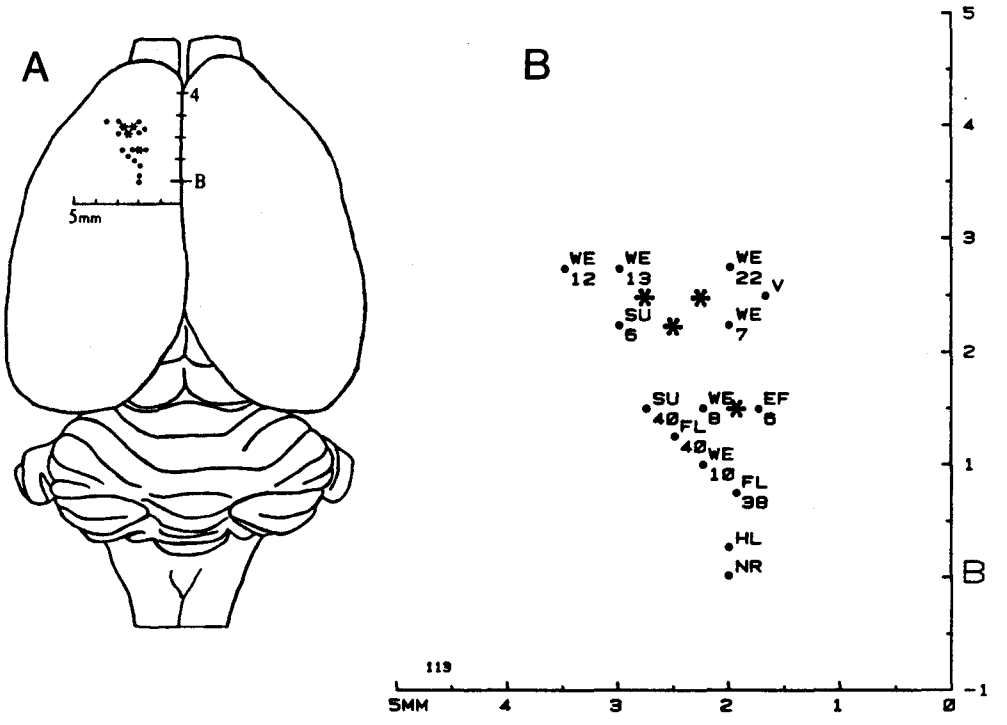
Vl - ventral lateral

Figure 1. Cortical injection site in non-lesion control animal #113.

A. Drawing of the dorsal view of the brain showing electrode penetrations (dots) and injection sites (*). B = bregma.

B. Diagramatic representation of electrode penetrations (dots) and injection sites (*). Numbers indicate threshold current values which elicited forelimb movements: EF = elbow flexion; FL = generalized forelimb response; HL = hindlimb; NR = no response; SU = supination; V = vibrissae; WE = wrist extension; B = bregma.

C. Camera lucida drawings of serial sections demonstrating the left forelimb motor cortical injection site of animal #113. The black area represents the dense accumulation of reaction product around the injection sites. Short lines represent retrogradely labeled cells. Fine dots indicate the distribution of anterograde labelling. Open arrow indicates section shown in fig. 2A.


A
4
B
5mm
B
WE 12
WE 13
SU 6
WE 22
V
WE 7
SU 40
WE 8
EF 6
FL 40
WE 10
FL 38
HL
NR
119
5MM
4
3
2
1
0
5
4
3
2
1
B
-1

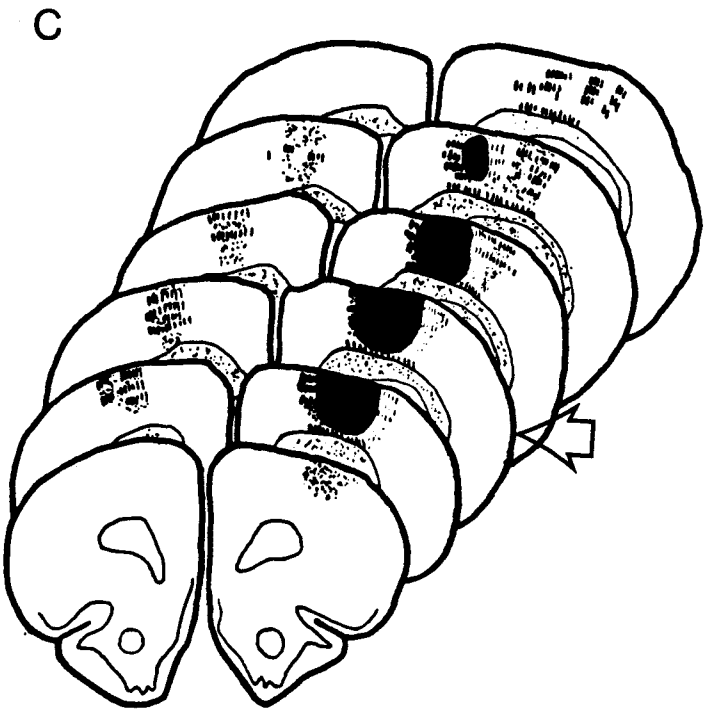
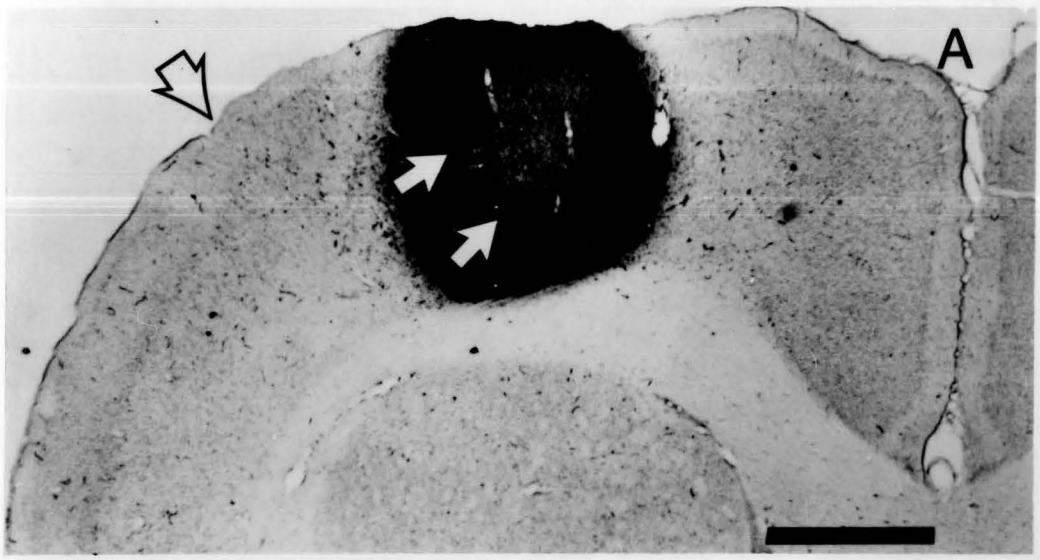

C

Figure 2.

A. Brightfield photomicrograph showing cortical injection of HRP into animal #113. White arrows indicate the 2 electrode penetrations which elicited low-threshold forelimb movements. The open arrow indicates the medial extent of the granular (somatosensory) cortex. Bar = 1 mm.

B. Brightfield photomicrograph through the frontal cortices of animal #063 showing an HRP injection into the left forelimb motor cortex. The large arrow in the right cortex indicates an electrode penetration which evoked forelimb movements. The small arrows indicate retrogradely labelled cell bodies. Anterograde labelling corresponds to the dark area superficial to the labelled cells and lateral to the electrode tract.


A

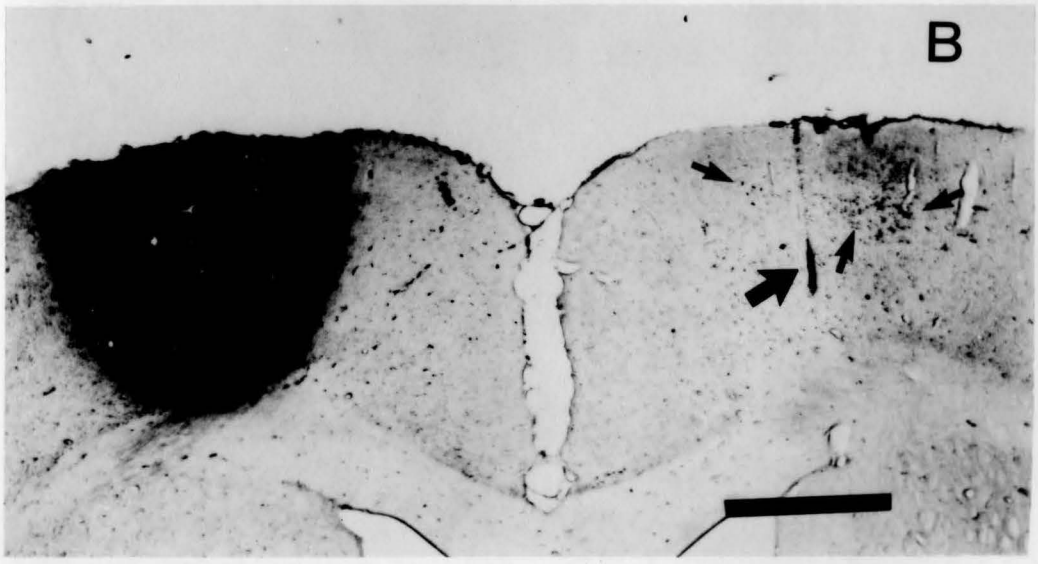

B

Figure 3. Camera lucida drawings of serial transverse sections (approximately 500 um apart) through the brainstem of animal #113 showing the distribution of reaction product after an HRP injection into the left forelimb motor cortex (figs. 1 and 2A). Large dots represent retrogradely labelled cell bodies. Fine dots represent anterograde labelling. Rectangles correspond to photomicrographs in figs. 7 and 8. Sections are arranged in a rostral to caudal sequence from A-X (fig. 3 continued on page 70)

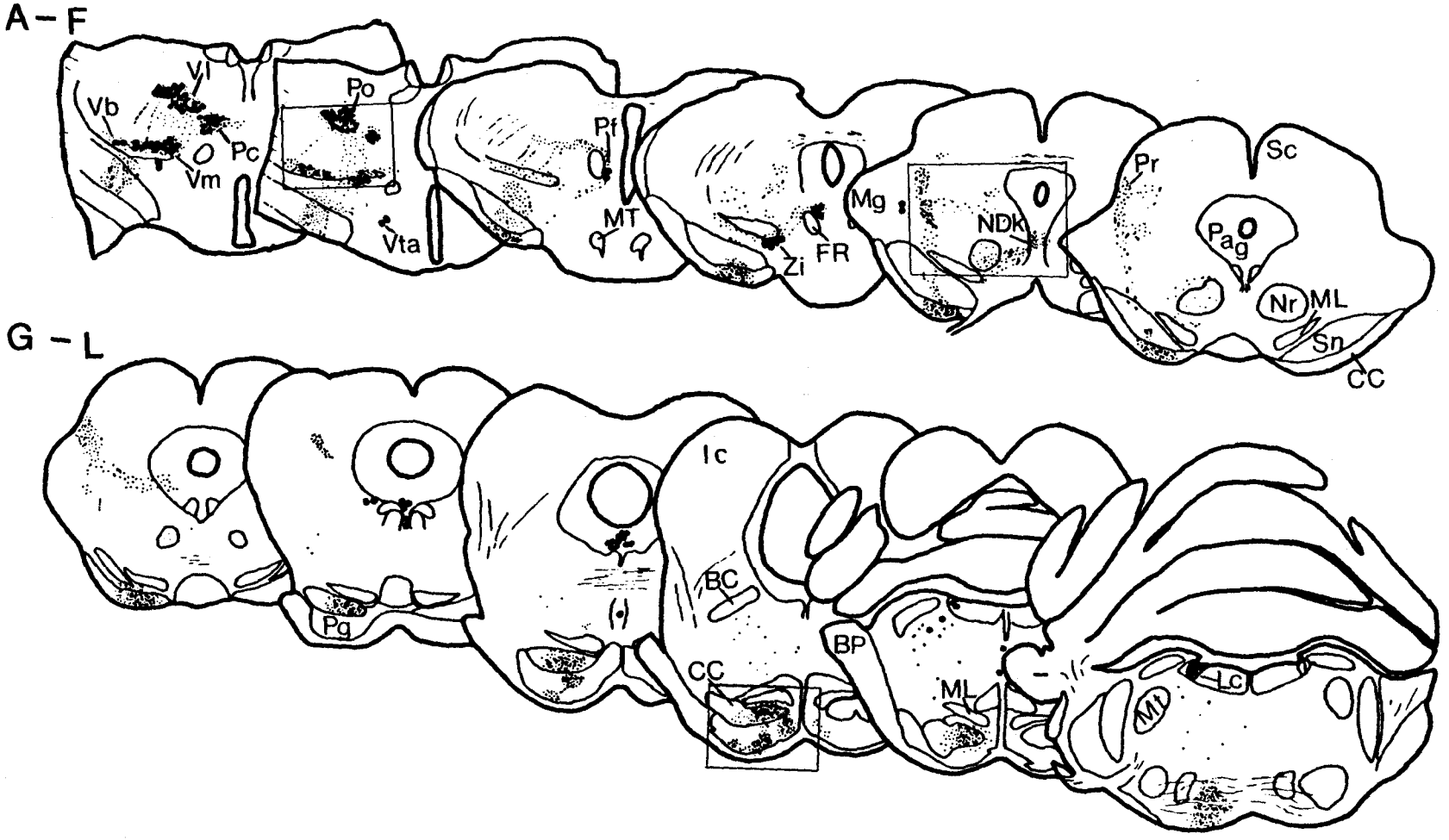

A – F
Vl
Vb
Po
Pc
Vm
Vta
Pf
MT
Zi
FR
Mg
NDk
Pr
Sc
Pag
Nr
ML
Sn
CC
G – L
Ic
BC
Pg
BP
CC
ML
Lc
ML

Figure 3. Continued. See page 67 for legend.

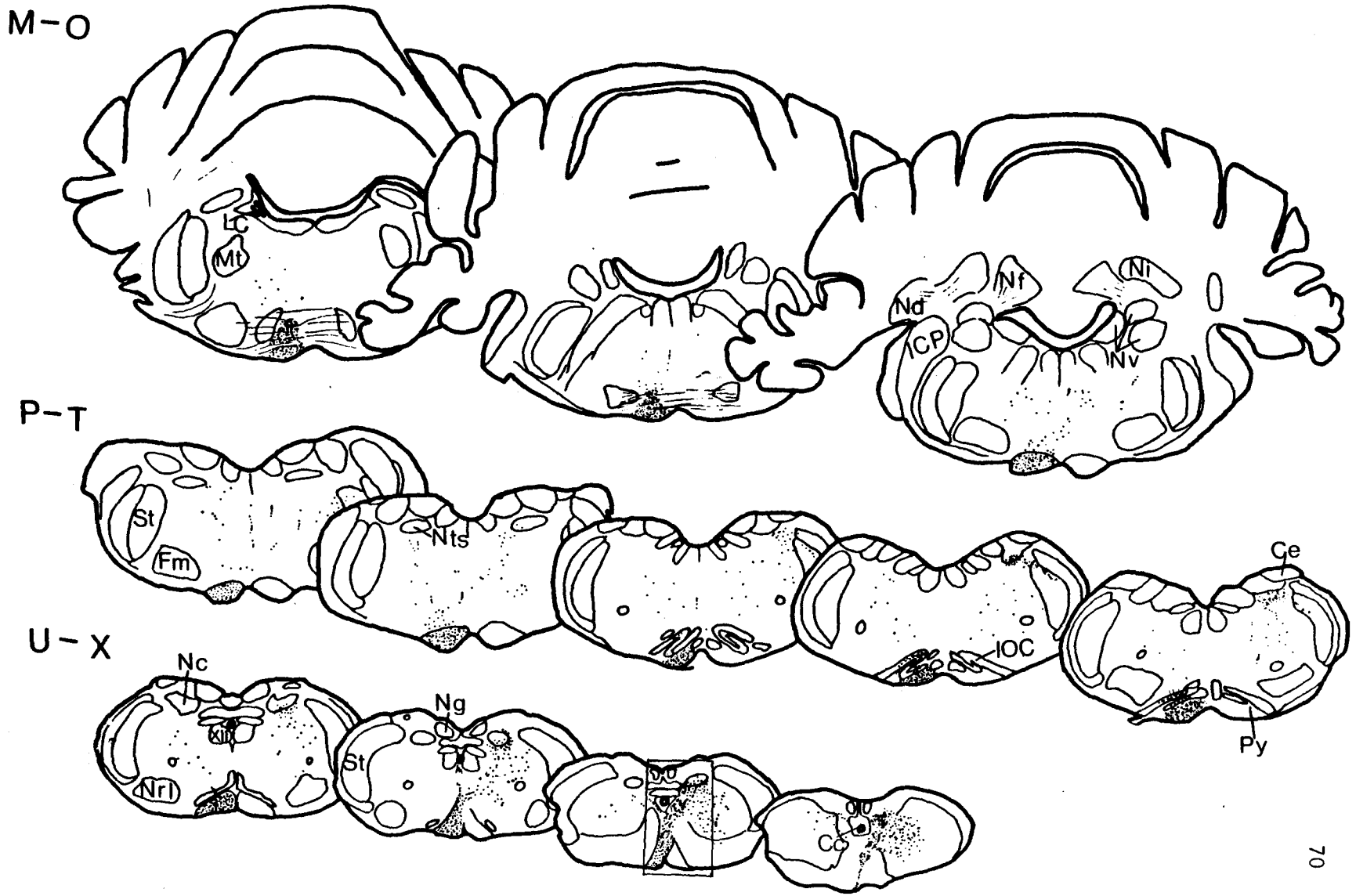
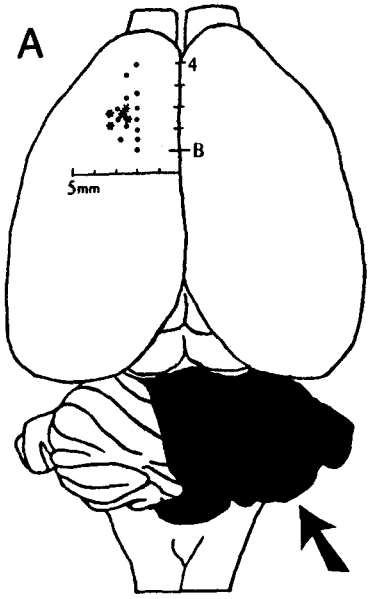

M–O
Lc
Mt
Nd
Nf
Ni
ICP
Nv
P–T
St
Fm
Nts
Ce
IOC
Py
U–X
Nc
Xii
Nrl
Ng
St
Cc

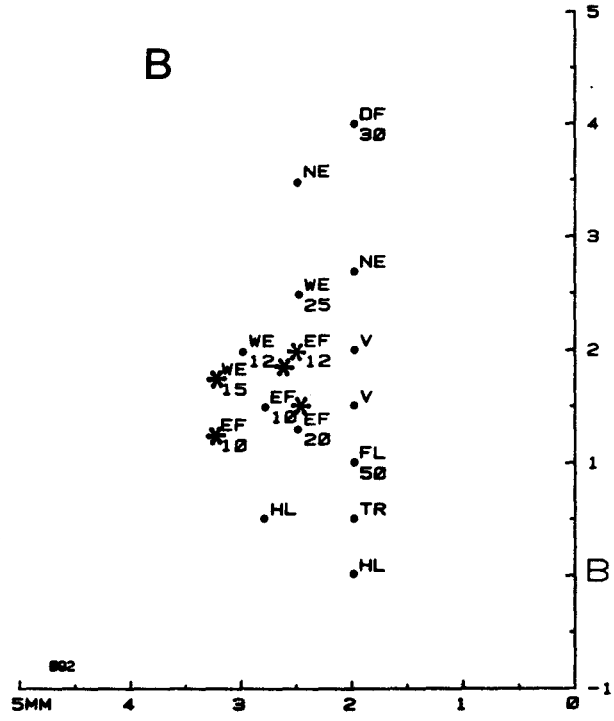
Figure 4. Cortical injection in adult animal #092 after neonatal hemicerebellectomy.

A. Dorsal view drawing showing the extent of the neonatal lesion (arrow) and all electrode penetrations (dots) as well as injection sites (*).

B. Diagramatic representation of electrode penetrations (dots) and injection sites (*). Numbers refer to the threshold currents which elicited contralateral movements. DF = digit flexion; EF = elbow flextion; FL = generalized forelimb movement; HL = hindlimb; NE = neck; V = vibrissae; WE = wrist extension; B = bregma.

C. Camera lucida drawings of serial sections (approximately 500 um apart) showing left forelimb motor cortical injection site. Sections are arranged in a rostral (lower left) to caudal (upper right) sequence. The black area represents the dense accumulation of reaction product around the injection sites. Short lines represent retrogradely labelled cells. Fine dots indicate the distribution of anterograde labelling.


A
4
B
5mm


B
DF
30
NE
NE
WE
25
WE
12
EF
12
V
WE
15
EF
10
V
EF
10
EF
20
FL
50
HL
TR
HL
B
5MM
4
3
2
1
0
5
4
3
2
1
-1

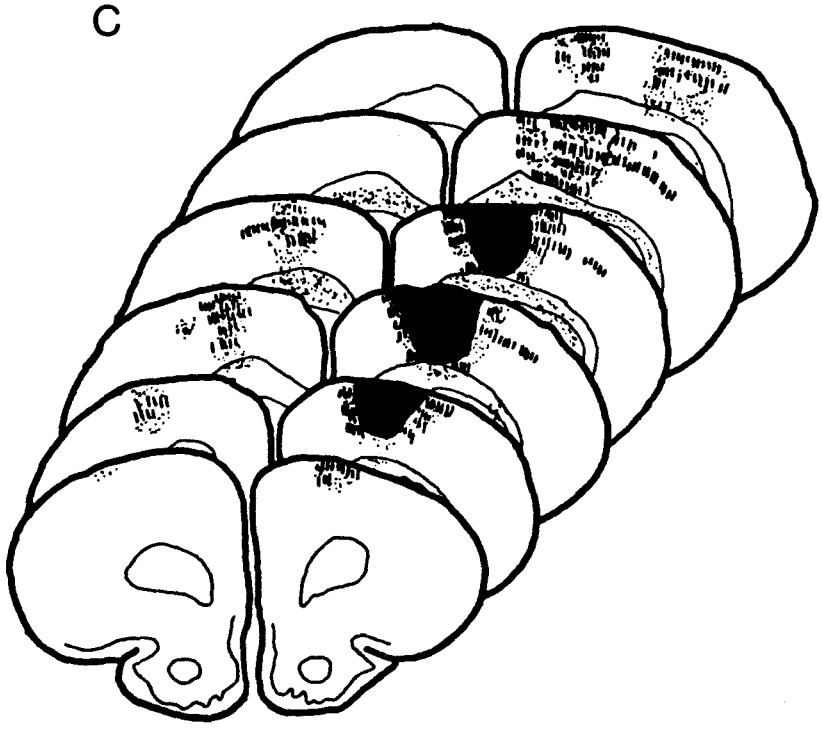

C

Figure 5. Camera lucida drawings of serial sections (approximately 500 um apart) through the brainstem of animal #092 showing the distribution of retrogradely labelled cells (large dots) and anterograde labelling (fine dots). The rectangles correspond to the photomicrographs in figs. 7 and 8. Sections are arranged in a rostral to caudal sequence from A-Y (fig. 5 continued on page 76).

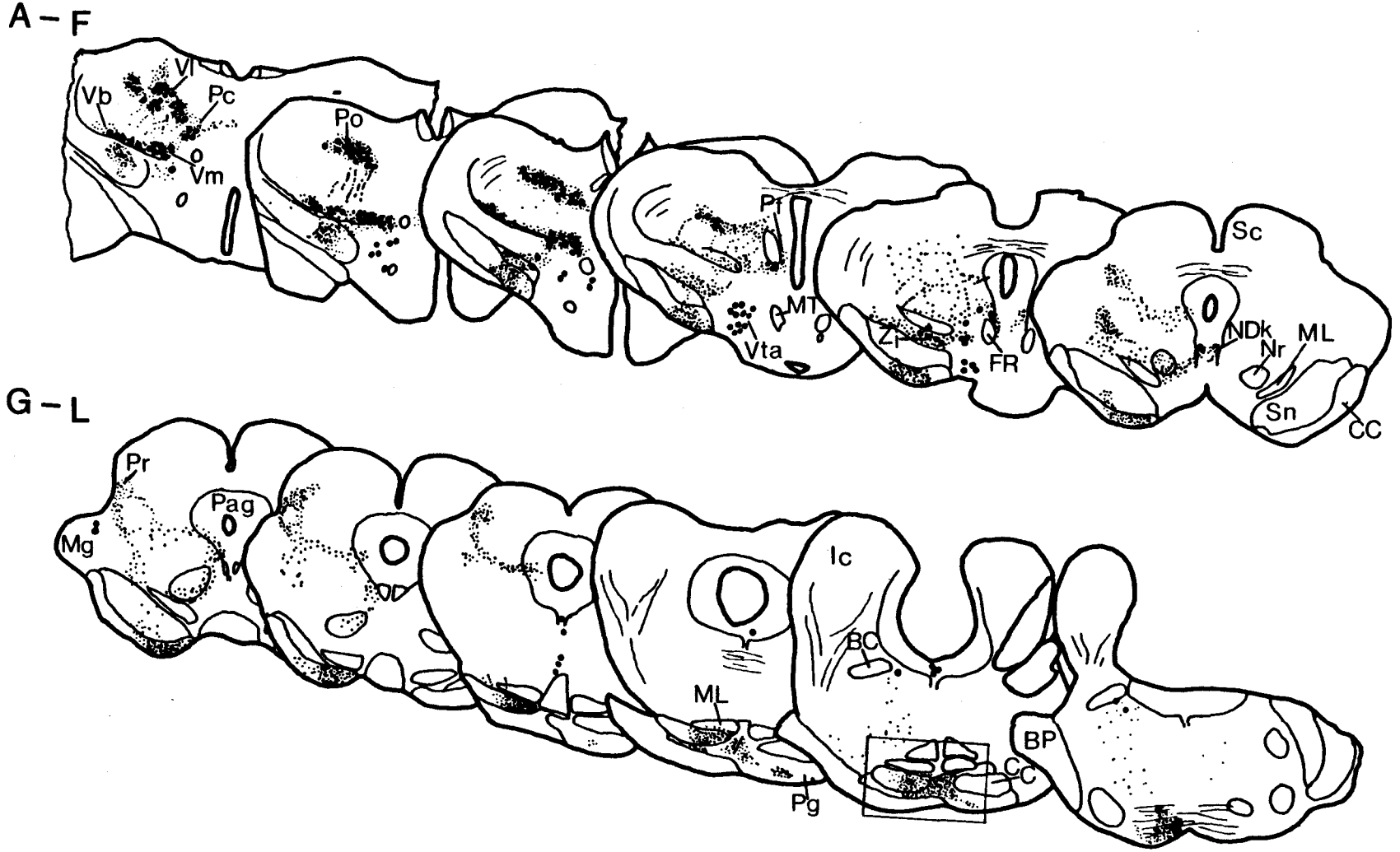

A – F
Vl
Vb
Pc
Po
Vm
Pf
MT
Vta
Zi
Q
FR
Sc
NDk
Nr
ML
Sn
CC
G – L
Pr
Pag
Mg
Ic
BC
ML
BP
CC
Pg

Figure 5. Continued. See page 73 for legend.

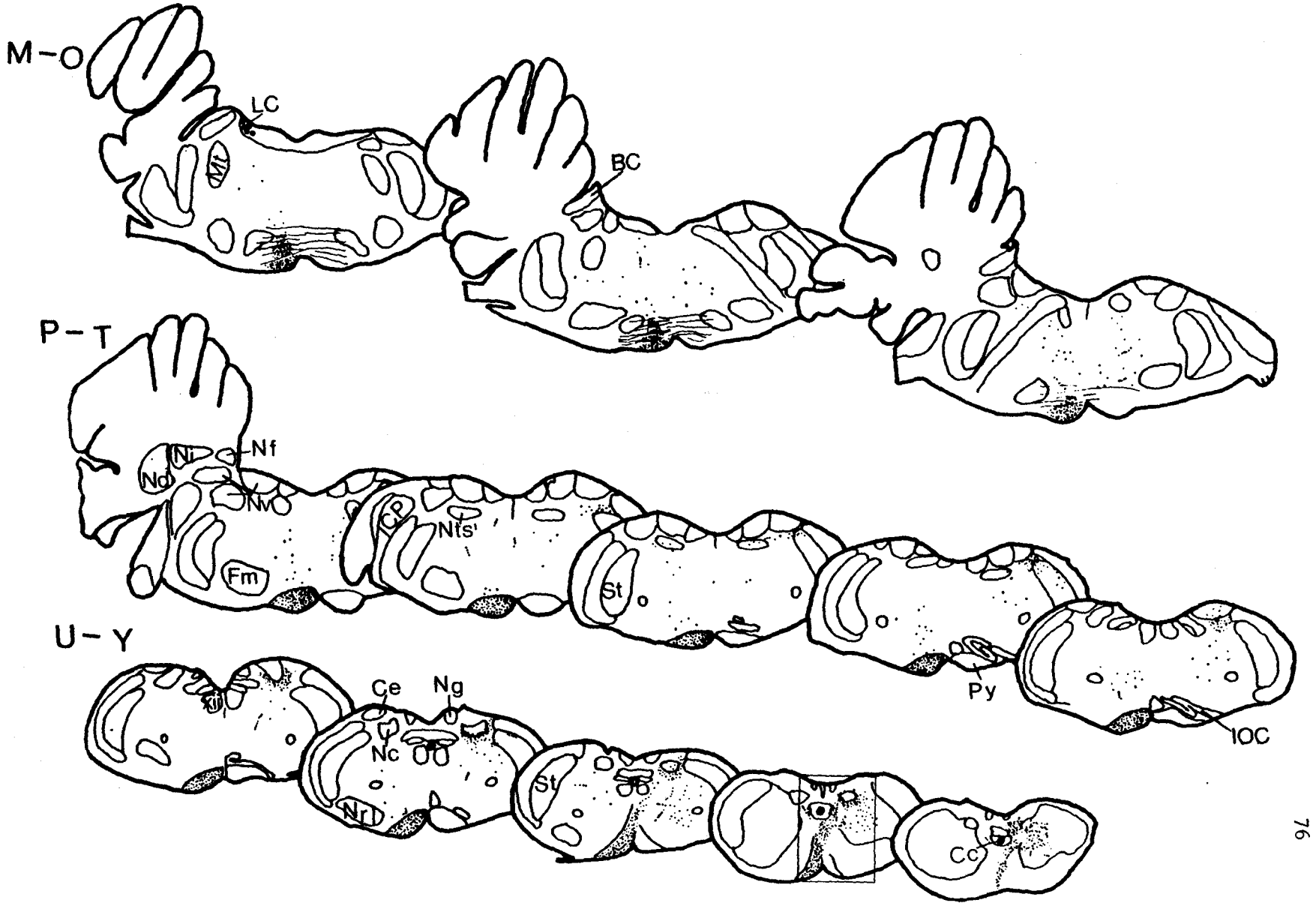

M–O
LC
Mt
BC
P–T
Ni
Nf
Nd
Nv
Fm
Nts'
St
Py
IOC
U–Y
Xil
Ce
Ng
Nc
Nr
St
Cc

Figure 6. Camera lucida drawing of a transverse section through the cervical spinal cord of animal #092 showing the distribution of anterograde corticospinal labelling (fine dots) after a left forelimb motor cortical injection (see fig. 4). The rectangle corresponds to the photomicrograph shown in fig. 8C.

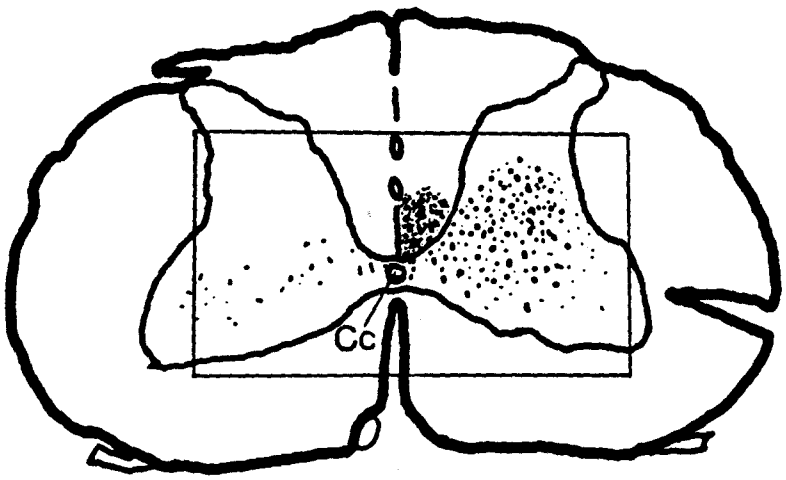

Cc

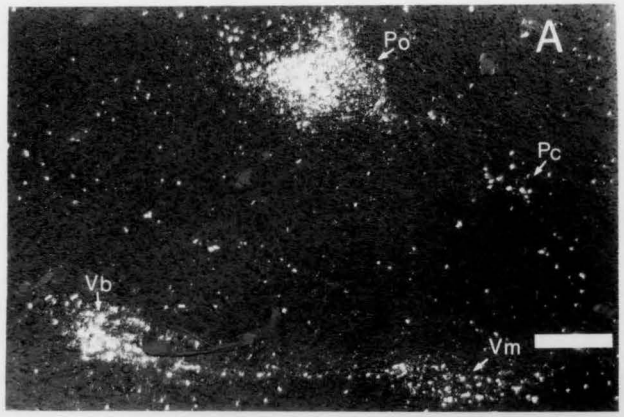
Figure 7. Polarized photomicrographs of transverse sections through the brainstem after motor cortical injections. HRP reaction product is white. Bars = 0.5 mm.

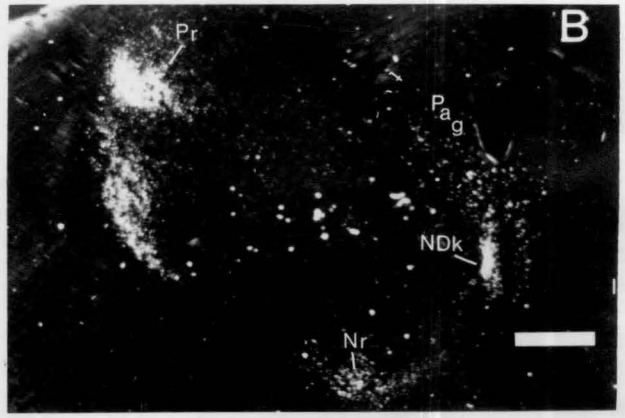
A. Corresponds to fig 3 section B showing retrogradely labelled cells (arrows) in caudal thalamic nuclei.

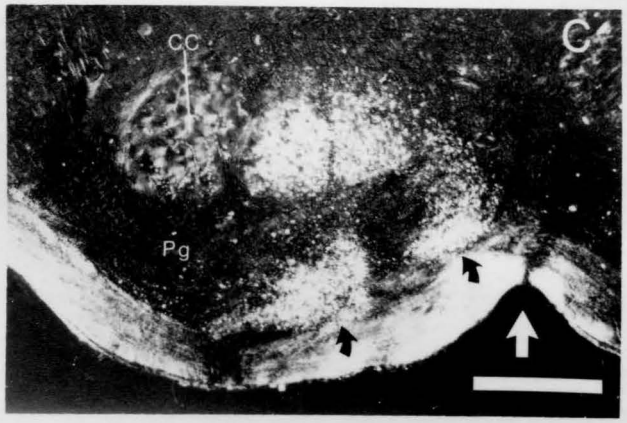
B. Corresponds to fig 3 section E showing anterograde labelling in midbrain.

C. Corresponds to fig 3 section J showing basilar pontine nuclei in a non-lesion animal. White arrow indicates the midline. Black arrows indicate columns of corticopontine labelling.

D. Corresponds to fig 5 section K showing basilar pontine nuclei in an adult after neonatal hemicerebellectomy. White arrow indicates the midline; curved, open arrows indicate aberrant contralateral corticopontine labelling.


A
Po
Pc
Vb
Vm


B
Pr
Pag
NDk
Nr


C
CC
Pg

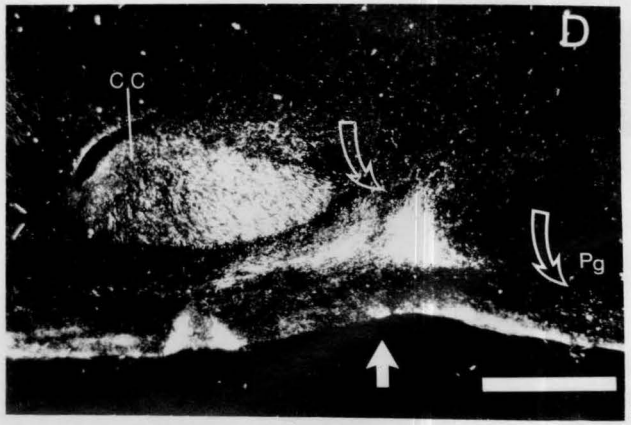

D
CC
Pg

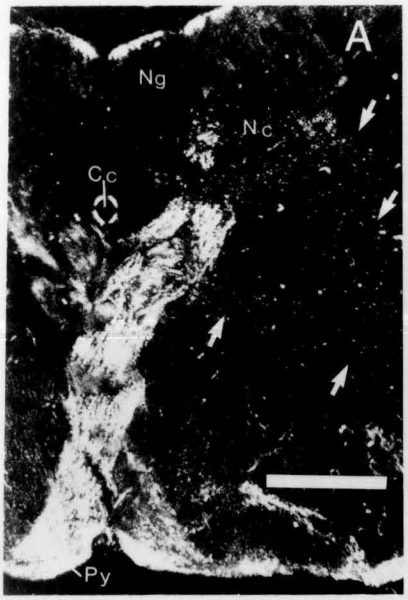
Figure 8. Photomicrographs of transverse sections through the brainstem and spinal cord after a left forelimb motor cortical injection as viewed with polarized light showing the HRP reaction product in white. Bars = 0.5 mm.

A. Pyramidal decussation corresponding to fig 3 section W of a noraml animal. The crossing is virtually complete. Arrows idicate corticoreticular labelling.

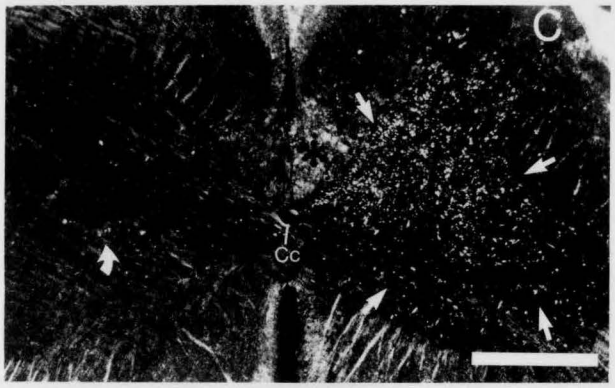
B. Pyramidal decussation corresponding to fig 5 section X in an adult animal after neonatal hemicerebellectomy. The crossing is virtually complete. Arrows indicate corticoreticular labelling.

C. Cervical spinal cord from a normal animal showing the location of the corticospinal tract in the dorsal funiculus (*). Straight arrows indicate the distribution of corticospinal fibers to the intermediate and ventral gray matter contralateral to the cortical injection. Curved arrow indicates the sparse ipsilateral corticospinal labelling.

D. Cervical spinal cord from an adult animal after neonatal hemicerebellectomy showing the location of the corticospinal tract in the dorsal funiculus (*). Straight arrows indicate the distribution of corticospinal fibers to the intermediate and ventral gray matter contralateral to the cortical injection. Curved arrows indicate sparse ipsilateral corticospinal labelling. Also see fig. 6.


A
Ng
Nc
Cc
Py


B
Ng
Nc
Cc
Py


C
Cc

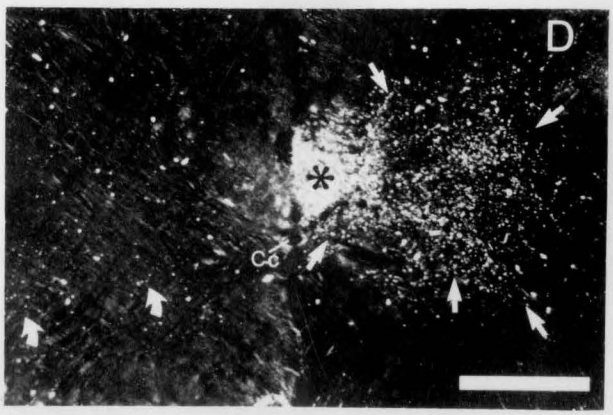
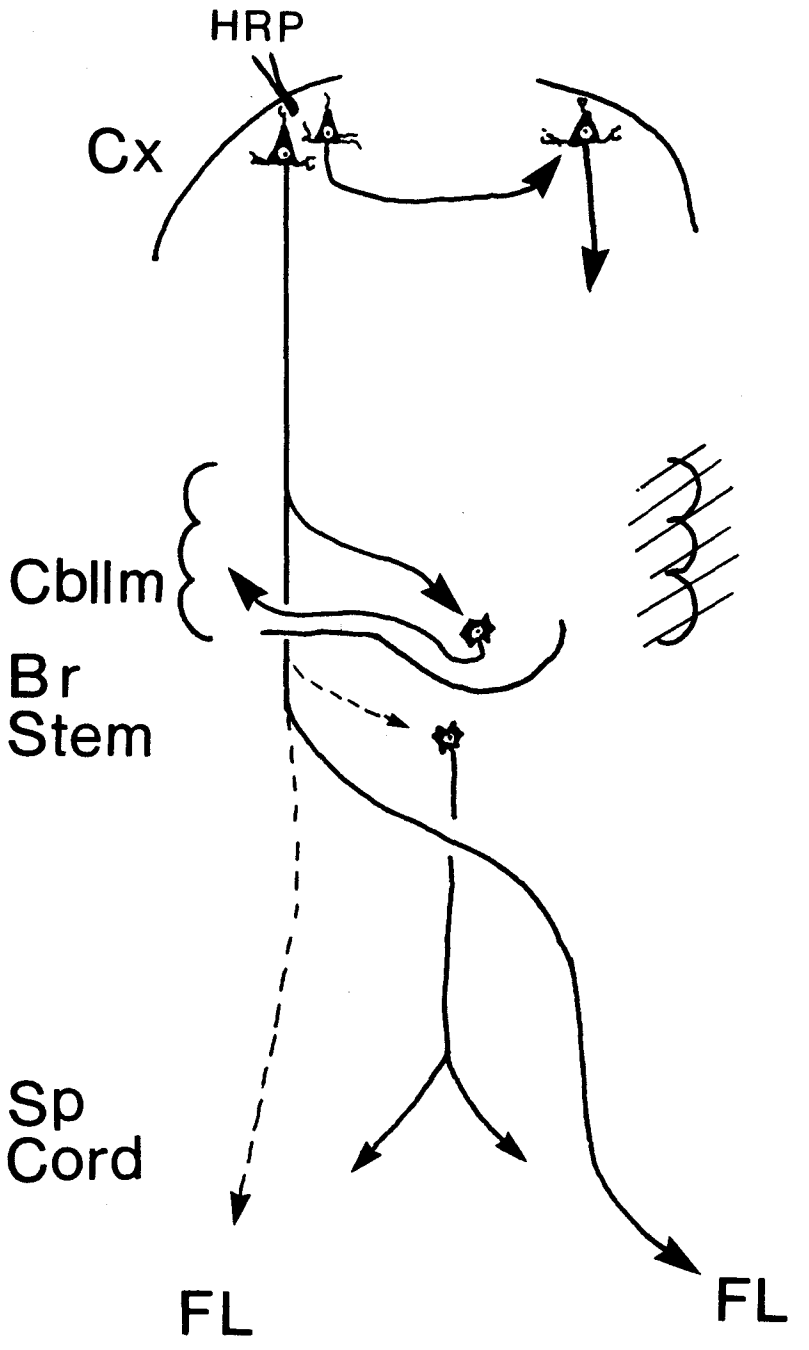

D
*
Cc

Figure 9. Summary diagram demonstrating possible ciruitry that might mediate cortically-evoked forelimb (FL) movements based on our anatomical findings in adult animals which had sustained neonatal hemicerebellectomy (hatched lines). Heavy lines indicate prominent projections and broken lines indicate smaller or sparce projections: Cx = cortex; Cbllm = cerebellum; Br Stem = brainstem; Sp Cord = spinal cord.


HRP
Cx
Cbllm
Br
Stem
Sp
Cord
FL
FL

The Effects of Secondary Lesions on Movements Evoked By Intracortical Microstimulation

ABSTRACT

These experiments were designed to determine which neuronal stuctures either may contribute to or mediate the low-threshold ipsilateral forelimb movements observed after neonatal hemicerebellectomy. Adult animals that had sustained neonatal cerebellar lesions received only one of four secondary lesions. Different animals received lesions of cerebellar tissue spared by the neonatal lesion, the corpus callosum, the opposite cerebral hemisphere or the medullary pyramid. Following these lesions intracortical microstimulation showed that secondary cerebellar or callosal lesions did not abolish the abnormal low-threshold responses evoked from the cerebral cortex. Thus the contalateral cortex or spared cerebellum do not mediate these responses. Secondary cortical lesions, although they caused a marked increase in the threshold currents for ipsilateral movements evoked from the intact cortex, seem to effect these responses only indirectly. Pyramidal lesions increased the threshold currents needed to elicit ipsilateral, as well as contralateral forelimb movements. This indicates that normal and abnormal low-threshold, cortically-evoked, forelimb responses are mediated by the corticospinal tract.

INTRODUCTION

Intracortical microstimulation in adult rats that sustained hemicerebellar lesions prior to weaning evoked ipsilateral forelimb movements at abnormally low current intensities (Expt. I). Since low-threshold currents normally only evoke contralateral forelimb movements (Kartje-Tillotson, et al., 1984), in correlation with the primarily crossed corticospinal tract (Valverde, 1966; Dunkerly and Duncan, 1969; Brown, 1971; Castro, 1975; Donatelle, 1977; Valhsing and Ferringa, 1980), the previous study (Expt. II) examined whether anomalous ipsilateral corticospinal fibers develop in response to neonatal hemicerebellectomy. Since corticospinal remodelling was not observed, the present experiment was designed to determine whether other neural structures may contribute or mediate the low-threshold ipsilateral forelimb movements observed after neonatal hemicerebellectomy.

The density of callosal connections between homologous motor cortical areas (Expt. II) suggests that stimulation of one cortex might activate the contralateral hemisphere and thereby evoke a limb movement ipsilateral to the stimulated cortex. Alternatively, the remodelling of motor corticopontine projections after neonatal hemicerebellectomy (Leong, 1977b, 1980; Mihailoff and Castro, 1981; Castro and Mihailoff, 1982; Expt. II)suggests that the spared cerebellar hemisphere may

contribute to ipsilateral forelimb responses. This possibility appears somewhat plausible in light of reported cerebellar efferent plasticity found after neonatal hemicerebellectomy (Lim and Leong, 1975; Leong, 1977a; Castro, 1978; Kawaguchi and Yamamoto, 1981; Tsukahara and Fujito, 1981). The possible contributions of the opposite cerebral cortex and the spared cerebellum to ipsilateral responses were examined in the present study by measuring threshold currents for movements after ablating the corpus callosum or the remaining cerebellar hemisphere in adult rats that had sustained neonatal hemicerebellectomy. Since low-threshold cortically-evoked movements were apparently not directly affected by these lesions, further work examined threshold currents for movements after medullary pyramidotomy. In this case, low-threshold responses were abolished.

MATERIALS AND METHODS

Seventeen, Long-Evans, black hooded male rats that sustained neonatal right hemicerebellectomy at 1-2 days of age were divided into four groups according to the placement of secondary lesions at 4-6 months of age. These secondary lesions included (1) the left cerebellar hemisphere to affect a complete two-stage cerebellectomy (n=4), (2) the rostral portion of the corpus callosum (n=4), (3) the right sensorimotor cortex (n=3) and (4) the left medullary pyramid (n=6). Two additional groups of animals sustained total neonatal cerebellectomy without a secondary adult lesion (n=3) or a left medullary pyramidotomy at maturity without a previous neonatal lesion (n=6).

In all animals sustaining lesions at maturity, threshold currents needed to evoke contra- and ipsilateral forelimb movements were measured before and after placement of adult lesions. Threshold currents for movements were also measured in those animals only receiving total neonatal cerebellectomy. Cortical microstimulation procedures were similar to those described in Expt. I. Animals were anesthetized with ketamine hydrochloride (100 mg/kg); the skull over the left frontal cortex was removed with a dental drill, and using bregma as a reference point, electrode penetrations were made into the left frontal cortex. The minimal current intensities needed to

consistently evoke contra- or ipsilateral forelimb movements (i.e., threshold currents) were determined. After this initial mapping, one of the four secondary types of lesions was made. When bleeding from the lesion had been controlled and the lesion site covered with gelfoam, the left cortex was re-mapped with electrode penetrations made either at or between previously mapped points where forelimb responses had been evoked. To minimize damage to the cortex being stimulated, the maximum current used was 100 uamps. Upon completion of intracortical stimulation, the animals were sacrificed by anesthetic overdose and vascular perfusion with saline followed by 10% buffered formalin. The brains were removed, and the extent of primary and secondary lesions were verified histologically. Frozen 40 um sections through the levels of lesion sites were cut and stained for myelin with cyanine R and counterstained for Nissl substance with neutral red.

Lesion Surgery

The neonatal lesion procedures are fully described in Expt. I. Neonatal cerebellar lesions were performed on animals anesthetized by hypothermia. The occipital bone was removed, the cerebellum was resected along the midline and the right half of the cerebellum was aspirated through a drawn glass pipette. After bleeding was controlled, the skin was sutured and the pup was then warmed under an incandescent lamp before being returned to its mother until weaning at three weeks of age.

Lesions in adult animals of the cerebellar tissue spared by the neonatal hemicerebellectomy were made by aspiration with a glass pipette after portions of the occipital bone were removed along with the underlying dura mater. In other animals, the corpus callosum was cut lateral to bregma with a small knife mounted onto a stereotaxic microdrive. The blade was lowered perpendicularly through the medial aspect of the right frontal cortex to a depth of 4mm. Four to five penetrations at slightly increasing angles away from the perpendicular plane were made. While raising and lowering the blade, care was taken not to disturb the superficial cortical vasculature. Lesions of the right frontal cortex were made by aspirations through a glass pipette.

Transection of the left medullary pyramid was made by a parapharyngeal approach. With the animal in a supine position in a stereotaxic instrument, a midline incision was made from the submandibular region to the suprasternal notch and the pretracheal muscles were reflected. The left superior laryngeal nerve and blood vessels were cauterized and resected. The trachea, esophagus and pharynx were retracted to the right without compromising respiration and the left prevertebral muscles were removed from the basi-occipital bone. With visualization aided by a dissecting microscope, a drill was used to remove a piece of bone from the midline crest to an area anterior to the condylar process. The medulla oblongata was thus exposed, and with a small knife the pyramid was cut medially from the basilar artery to the first large blood vessel laterally. The cut

edges of the pyramid were then pushed apart with the side of the knife to insure that the pyramidotomy was complete. Gelfoam was placed over the bone defect and the wound was closed with surgical clips.

After pyramidotomy, the animal was rotated back to the prone position for cortical stimulation. To insure that the preparation had not deteriorated, three or four electrode penetrations were made into the right frontal cortex, corresponding to the intact pyramid. If left forelimb movements could be evoked from these right cortical penetrations at current intensities below 15 uamps, stimulation of the left cortex was initiated. Following left cortical stimulation procedures, the right cortex was again stimulated to determine the state of the preparation.

RESULTS

All neonatal lesions included the right cerebellar cortex, white matter and deep cerebellar nuclei with varying involvement of the vermis (fig. 1A and fig. 3A). Prior to the placement of the secondary lesions at maturity, microstimulation of the left frontal cortex evoked bilateral, low-threshold forelimb movements, similar to data presented in Expt. I (fig. 2). Comparable low-threshold forelimb responses were observed in adult animals that had sustained complete neonatal cerebellectomy (fig. 1B and fig. 2).

Secondary lesions of cerebellar tissue spared by neonatal hemicerebellectomy included most of the posterior lobe with variable involvement of the deep cerebellar nuclei; the largest lesions removed all the deep nuclei (fig. 3B). Intracortical microstimulation after placement of secondary cerebellar lesion revealed no changes in threshold values. Ipsilateral forelimb responses could still be elicited at abnormally low current intensities (fig. 4) and were found at all electrode penetrations. Similar findings were observed after secondary callosal lesions; low-threshold ipsilateral responses were still present at over 90% of the electrode penetrations (fig. 5). Although histological analysis in these animals demonstrated incomplete transection of the rostral corpus callosum, that portion of the corpus callosum presumed to transmit callosal connections between forelimb

motor areas (based on anatomical findings, Expt. II), was transected (fig. 3C).

Secondary Cortical and Medullary Pyramidal Lesions

In contrast to findings after secondary cerebellar or callosal lesions, intracortical stimulation of the left motor cortex after secondary right cortical lesions revealed an increase of threshold currents (mean = 43 uamps, S.D. = 23.1) needed to evoke ipsilateral forelimb movements. In addition, only 30% of the penetrations that had showed ipsilateral responses prior to the cortical lesion showed ipsilateral responses afterwards. Contralateral forelimb movements were still observed at low current intensities (fig. 6). These findings were consistent in spite of considerable variation in the secondary cortical lesions (fig. 3D).

After secondary medullary pyramid lesions in adult animals that had sustained neonatal cerebellar lesions, fewer contra- and ipsilateral forelimb responses were evoked at current intensities of less than 100 uamps in areas of the left cortex that gave forelimb responses prior to the lesion (fig. 8). The threshold currents needed to evoke responses were considerably elevated for both contra- (mean = 55 uamps, S.D. = 23) and ipsilateral (mean 54 uamps, S.D. = 22) forelimb movements (fig. 7) in comparison to pre-pyramidotomy values (contra- mean = 9.3 uamps, S.D. = 3.2; ipsi- mean = 22.6 uamps, S.D. = 13) (fig 7). Furthermore, stimulation of the right cortex, corresponding to the intact pyramid, showed contralateral forelimb

responses at normal threshold current values (mean = 10 uamps, S.D. = 3.5). Right forelimb movements evoked from the right motor cortex, after left pyramidotomy, were found at 28% (normally 99% of forelimb cortical penetrations give ipsilateral responses; fig. 8A) of the penetrations with a mean threshold current value of 68 uamps, S.D. = 12.

The responses evoked upon stimulation of the left cortex, after a left pyramid lesion in a normal adult rat, were similar to those found after pyramidotomy in adult animals that previously sustained neonatal hemicerebellectomy. Fewer contra- and ipsilateral forelimb responses were observed (indicated by the increase in percent no response as illustrated in fig. 9B). Contralateral responses demonstrated a large increase in threshold current values (mean = 63.8 uamps, S.D. = 22) when compared with pre-lesion data (mean = 9.9 uamps, S.D. = 1.25). Although the mean threshold value for the ipsilateral responses in control animals after pyramidotomy was 40 uamps (S.D. = 18.8) as compared to 38 uamps (S.D. = 11) for non-lesion control animals (Expt. I), there was a large shift in the distribution of threshold responses (fig. 9A and B). Stimulation of the right motor cortex, corresponding to the intact pyramid, evoked contralateral forelimb responses at low-threshold currents (mean = 9.3 uamps, S.D. = 2.0), while ipsilateral movements occurred at a mean value of 54 uamps, S.D. = 2.1. In additon, only 58% (as compared to 96% in non-lesion controls) of the electrode penetrations where contralateral forelimb

responses were evoked.

Histological analysis, using sections cut in either the coronal or saggital plane (fig. 3E and F), showed that the left pyramid was consistently transected at levels just rostral to the inferior olive. While there may have been some sparing of pyramidal fibers, it was difficult to detect such sparing in histological sections; physiological findings were consistent among animals. The largest lesions slightly encroached upon the ventral tegmentum. Only slight damage to the right pyramid was observed in one animal.

DISCUSSION

Placement of secondary cerebellar or callosal lesions in adult rats that sustained neonatal hemicerebellectomy did not abolish the abnormal, low-threshold, ipsilateral forelimb movements evoked by intracortical stimulation. In contrast, secondary cortical lesions caused a marked increase in the threshold currents needed to evoke ipsilateral forelimb responses. Pyramidal lesions increased the threshold currents needed to elicit both ipsilateral as well as contralateral forelimb movements; additionally, the number of loci that elicited movements was considerably reduced when compared to animals without pyramidal lesions (see fig. 10).

The failure of secondary cerebellar lesions to affect the level of threshold currents needed to evoke ipsilateral forelimb movements indicates that aberrant corticopontine (Leong, 1977b; Castro and Mihailoff, 1982; Expt. II) and cerebellofugal fibers (Lim and Leong, 1975; Leong, 1977a; Castro, 1978; Kawagucki and Yamamoto, 1981; Tsukahara and Fujito, 1981; Gramsbergen and Ijkma-Paassen, 1982) observed after neonatal hemicerebellectomy do not directly contribute to the evoked forelimb movements. These findings are not surprising since neuroanatomical remodelling was not found after lesions in 15 day old rats (Leong, 1977a) whereas low-threshold ipsilateral movements were observed after similar lesions in 21 day old rats (Expt. I). The

presence of low-threshold ipsilateral movements after complete cerebellectomy in the newborn further discounts the mediation of the observed responses through the spared cerebellar hemisphere.

Persistence of low-threshold, ipsilateral forelimb movements after callosal lesions suggests that cortical stimulation does not mediate the ipsilateral movements by activation of the contralateral hemisphere via the corpus callosum. However, ablation of the opposite cortex did raise the current thresholds needed to evoke ipsilateral movements by stimulation of the unablated motor cortex. Distribution of ipsilateral responses after cortical lesion suggests that corticospinal projections from the opposite hemisphere help produce a baseline of activity within the spinal cord on the side ipsilateral to the stimulated cortex. This baseline of activity is likely not to be affected by callosal lesions but would be reduced by cortical ablation (Gilman and Marco, 1971; Gilman, et al., 1971, 1974). As a result, more current would be necessary to evoke a movement of the forelimb ipsilateral to the stimulated cortex (opposite the ablated cortex), exactly as observed.

The same line of reasoning applies to the results seen also in animals where right cerebral cortex was stimulated after a left medullary pyramidotomy. In this situation, corticospinal inputs to the side of the spinal cord ipsilateral to the stimulated cortex were disrupted and, again, higher current intensities were needed to evoke ipsilateral forelimb movements while the contralateral forelimb

responses occurred at normal threshold values. Finally, if stimulation of the left cerebral cortex activates (through callosal fibers) the opposite cortex which in turn mediates a forelimb response to the spinal cord ipsilateral to the stimulated cortex, then a left pyramidotomy should not affect the ipsilateral forelimb response. However, a pyramidal lesion increased the threshold current for both ipsilateral and contralateral movements, and thereby further indicated that the corpus callosum does not mediate forelimb responses ipsilateral to the stimulated cortex.

In agreement with several previous reports (Barron, 1934; Woolsey, 1972; Asanuma, et al., 1980; Gorska, et al., 1980; Castro, et al, 1984), cortical stimulation on the side corresponding to a unilateral pyramidotomy in control animals caused an elevation in threshold current intensities necessary to evoke contralateral forelimb movements. Medullary pyramidotomy similarly affects threshold currents evoking contralateral responses in adult animals after neonatal hemicerebellectomy. These findings correspond to the primarily crossed laterality of the rodent corticospinal tract (Valverde, 1966; Dunkerly and Duncan, 1969; Brown, 1971; Castro, 1975; Donatelle, 1977) which has also been described in numerous studies on several other species (Heffner and Masterton, 1975; Armand, 1982). Regarding the ipsilateral movements which are evoked at abnormally low current thresholds after neonatal hemicerebellectomy, a significantly higher threshold current was needed to evoke these movements after pyramidotomy. The anatomical

basis for these findings is not clear since no anomalous ipsilateral corticospinal fibers which might have been transected by pyramidotomy were found after neonatal hemicerebellectomy (Expt. II).

The lack of corticospinal or corticobulbar plasticity (Expt. II) that might correspond to the observed low threshold ipsilateral forelimb movements suggests that the responses are mediated via normal corticospinal fibers. Possibly alterations of excitability at spinal cord levels may occur in response to neonatal cerebellar lesions which could explain the low-threshold ipsilateral forelimb movements evoked by intracortical microstimulation.

Figure 1.

A. Dorsal view of the brain of an adult rat that sustained a neonatal hemicerebellectomy. Arrows indicate margins of tissue spared by neonatal lesion.

B. Dorsal view of the brain of an adult rat that sustained a neonatal cerebellectomy.


B

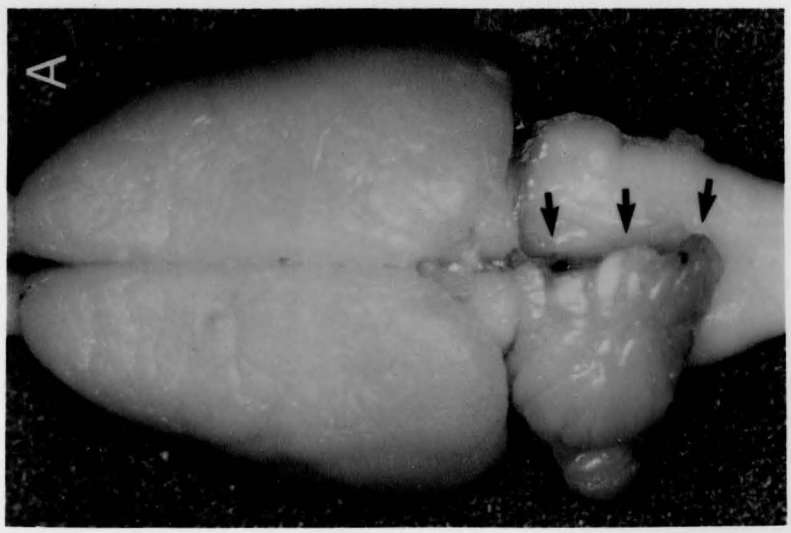

A

figure 2. Histogram comparing the mean threshold currents for adult animals that had sustained neonatal hemicerebellectomy (to the left) and animals that sustained cerebellectomy (to the right). The open column represents contralateral responses while the black column represents ipsilateral movements. The bar = 1 S.D. All following histograms are similar in construction.

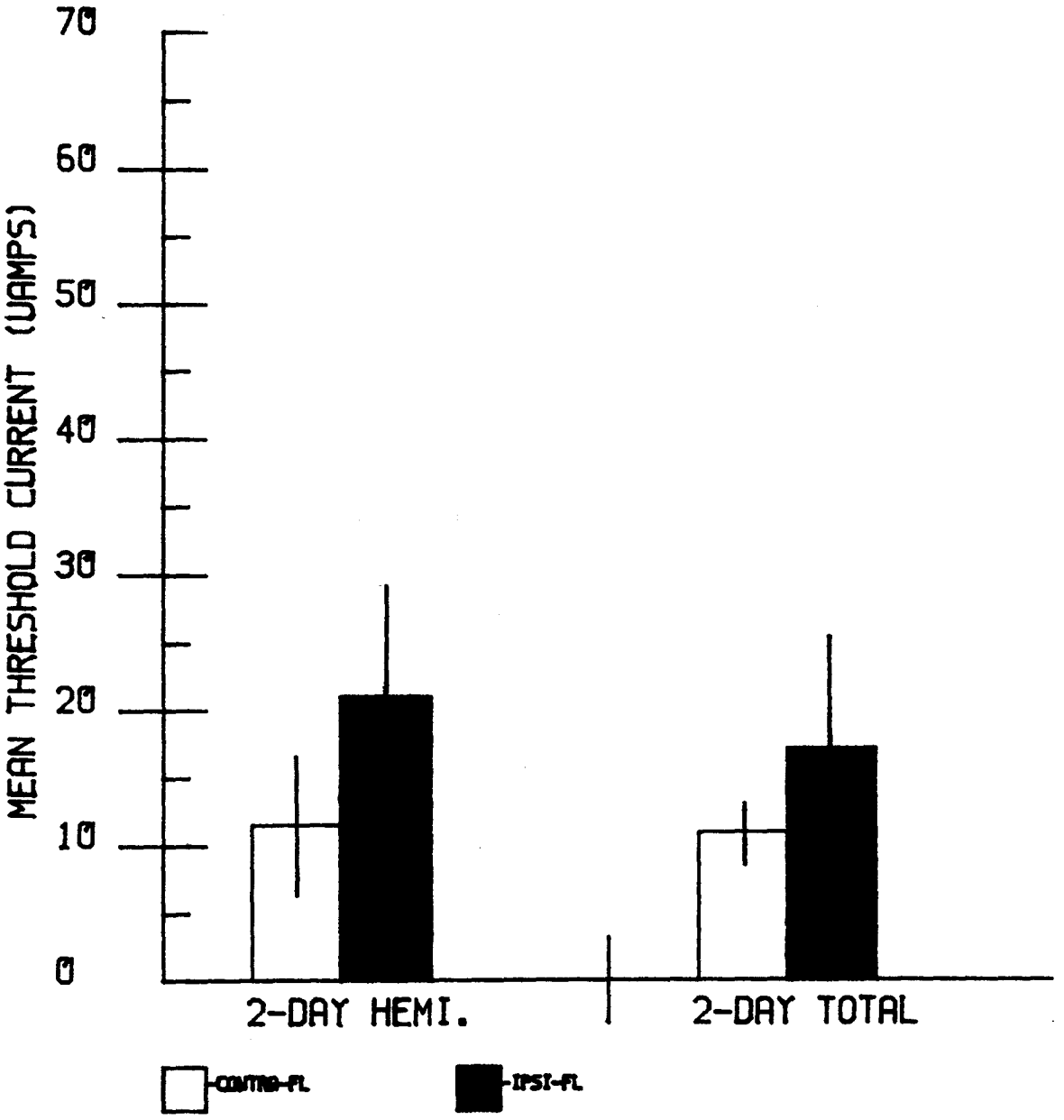

70
60
50
40
30
20
10
0
MEAN THRESHOLD CURRENT (UAMPS)
2-DAY HEMI.
2-DAY TOTAL
CONTRA-FL
IPSI-FL

Figure 3.

A. Transverse section through the metencephalon of an adult animal after neonatal hemicerebellectomy. Arrow indicates margin of cerebellar tissue spared by the neonatal lesion.

B. Transverse section through the metencephalon of an adult animal (#116) that sustained neonatal hemicerebellectomy and secondary adult cerebellar lesion. Arrows indicate the dorsal extent of tissue spared by adult cerebellar lesion.

C. Coronal section through the right frontal cortex of an animal (#094) that sustained a secondary callosal lesion (arrows).

D. Coronal section through the right frontal cortex of an animal (#112) that sustained a secondary cortical lesion (arrows).

E and F. Saggital and transverse sections through the medulla of an animal that sustained a secondary lesion through the pyramid (arrow).

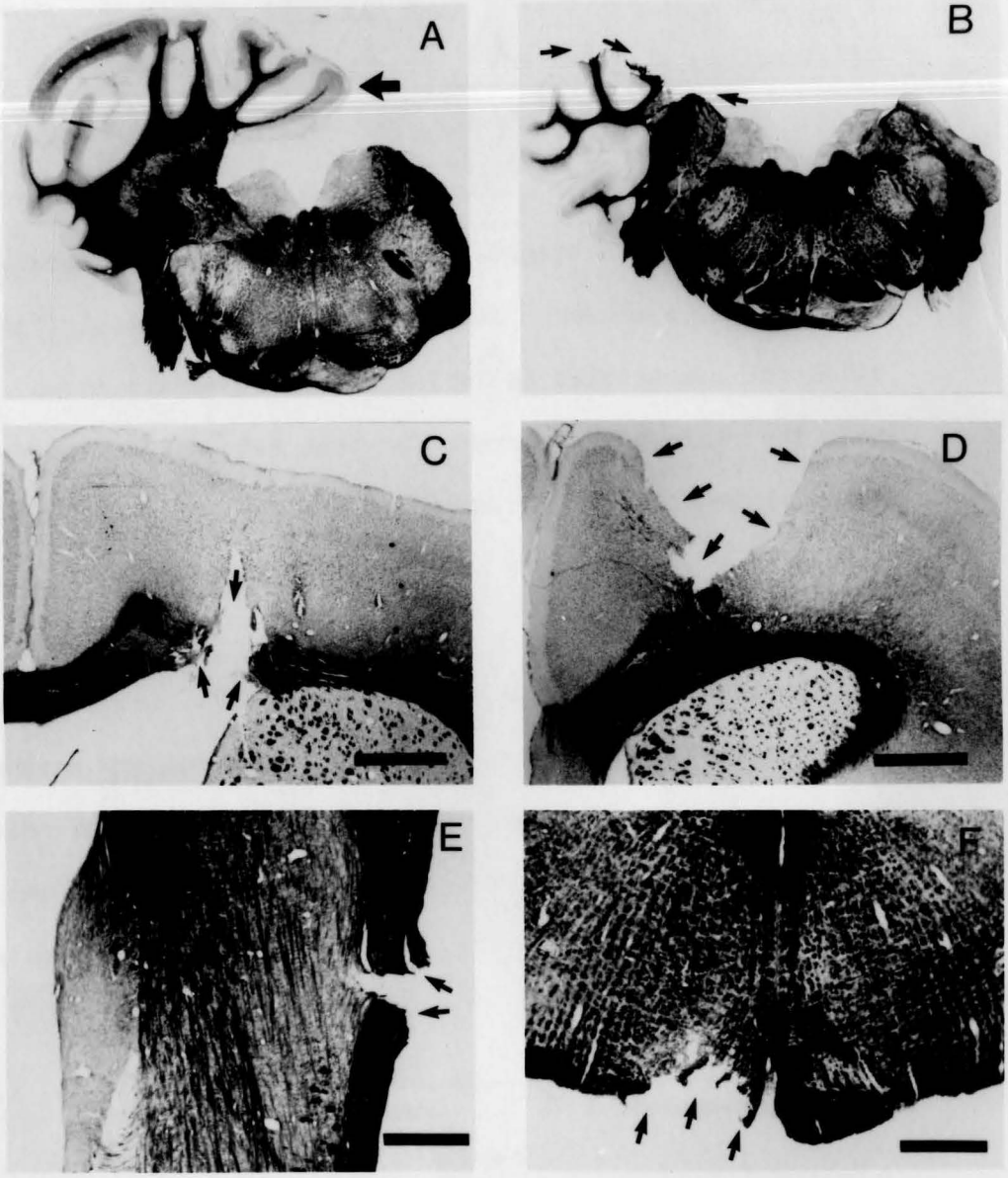
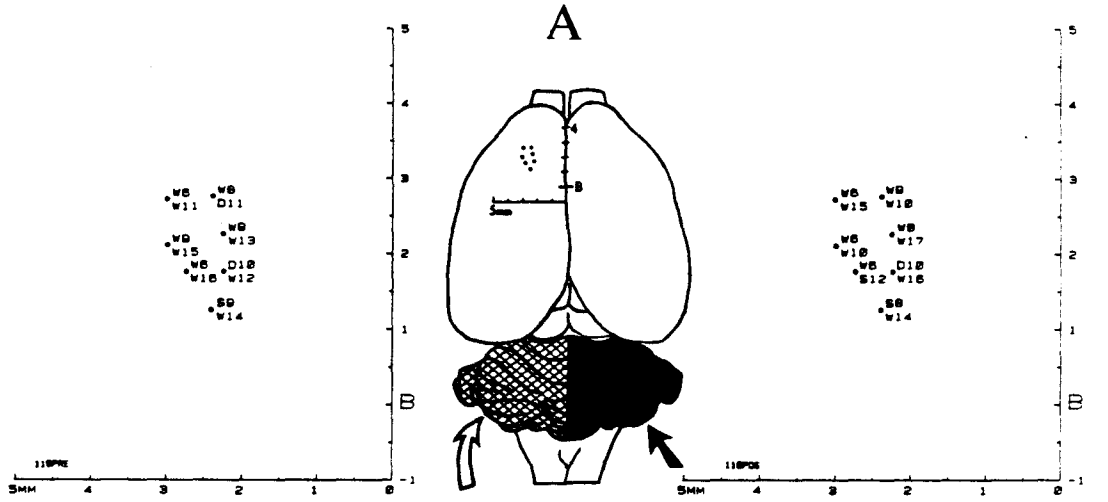

A
B
C
D
E
F

Figure 4.

A. Drawing of the dorsal view of the brain to show the orientation of electrode penetrations (dots),in an animal (#116) that sustained a neonatal hemicerebellectomy (black arrow) followed by a secondary cerebellar lesion at maturity (open arrow). B = bregma. Pre- (to the left) and post- (to the right) secondary lesion data are presented. For each electrode penetration (point) the contralateral joint moved and the threshold current for that response are shown over the ipsilateral joint moved with the threshold current (uamps): D = digits; E = elbow; NR = no response; S = shoulder; W = wrist.

B. Histogram of the data obtained from the animals before (to the left) and after (to the right) secondary cerebellar lesion. Open column represents the mean threshold current for the contralateral response and the open column, the ipsilateral response (bar = 1 S.D.). Pre- and post-adult lesion data are similar.

A



B

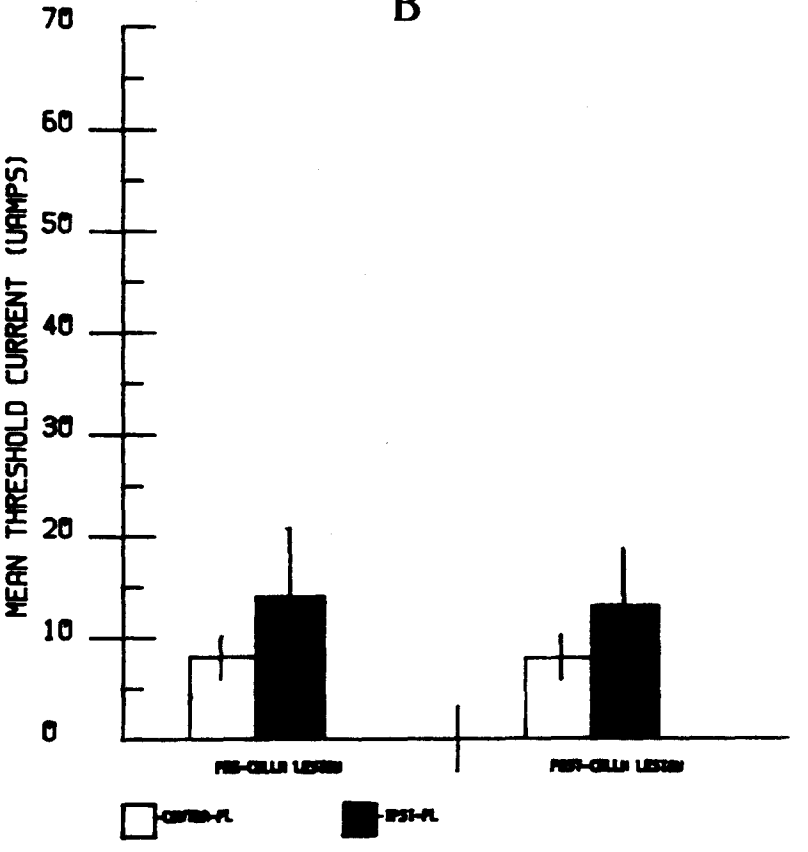
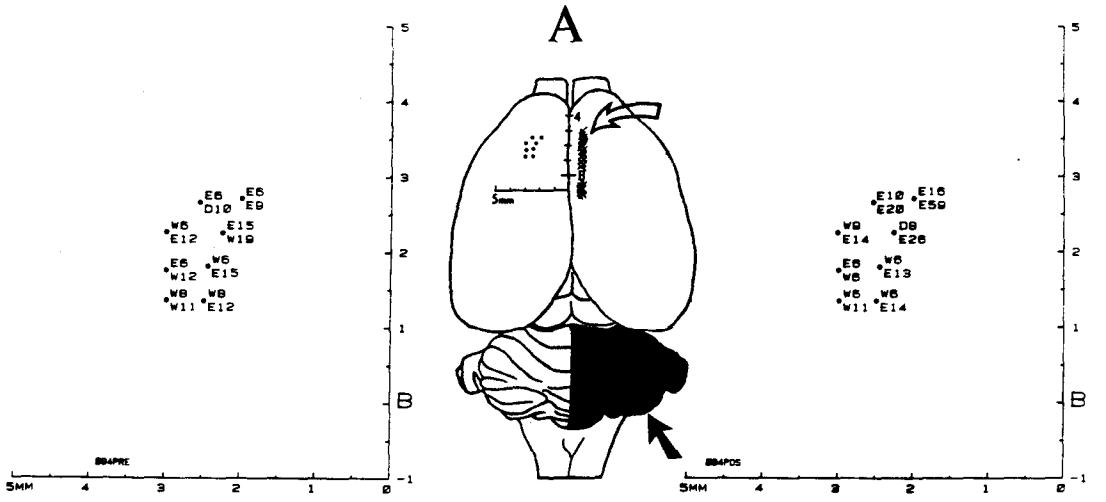


Figure 5.

A. Pre- (to the left) and post- (to the right) callosal lesion (open arrow) data from an adult animal (#094) that had sustained a neonatal hemicerebellectomy (closed arrow). The data are represented as descibed in fig. 4.

B. Histogram showing a comparison of the group data for pre- (to the left) and post- (to the right) callosal lesion stimulation (bar = 1 S.D.). No difference was found between these data.


A
E6 E5
D10 E9
W6 E15
E12 W10
E6 W6
W12 E15
W8 W8
W11 E12
E10 E16
E20 E59
W9 D8
E14 E26
E6 W6
W6 E13
W6 W6
W11 E14
5MM
B
5mm

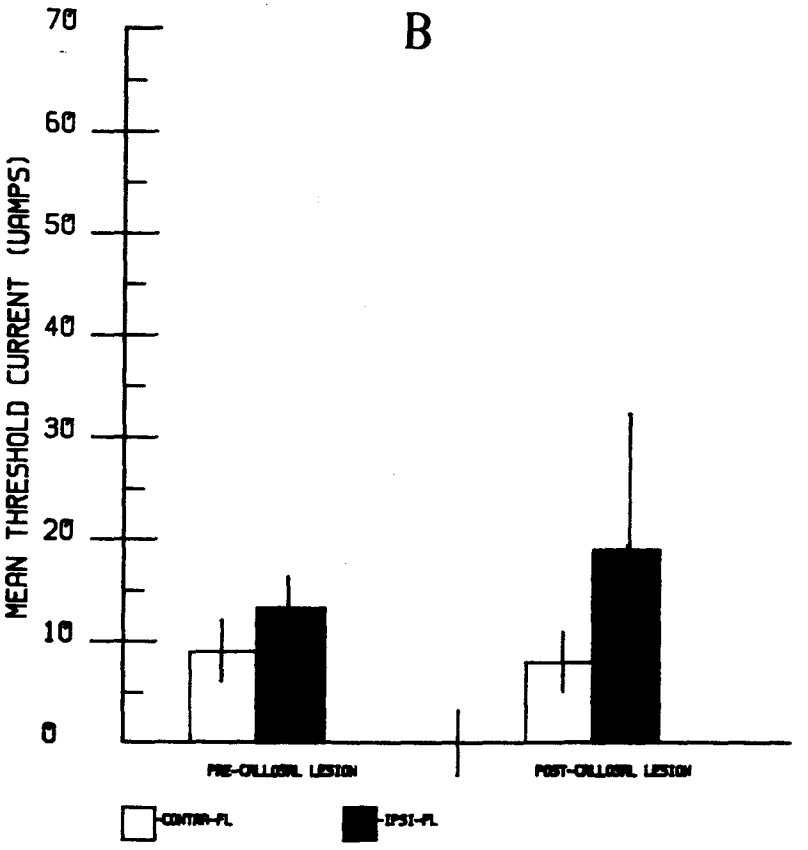
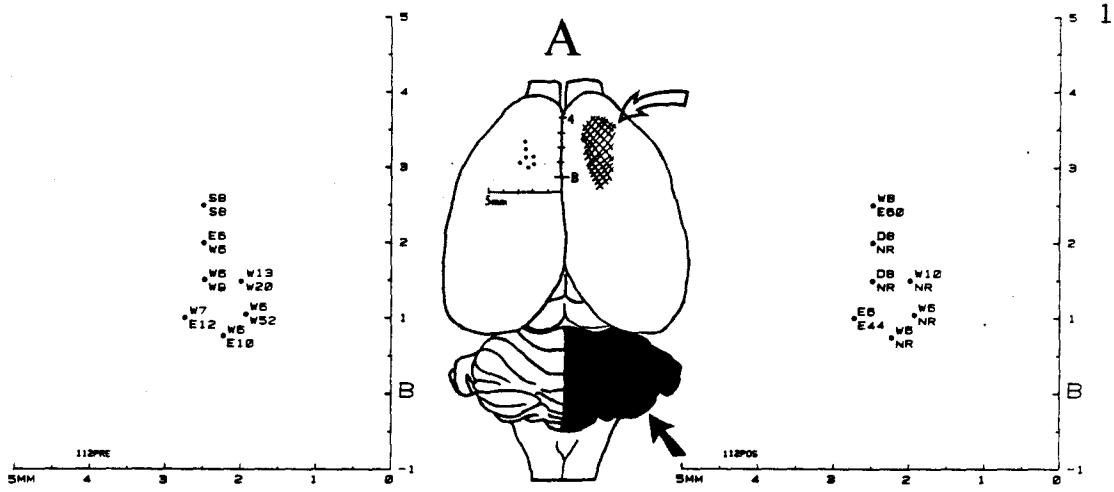

B
MEAN THRESHOLD CURRENT (UAMPS)
70
60
50
40
30
20
10
0
PRE-CALLOSAL LESION
POST-CALLOSAL LESION
CONTRA-PL
IPSI-PL

Figure 6.

A. Pre- (to the left) and post- (to the right) cortical lesion (open arrow) data from an animal (#112) that had sustained a neonatal hemicerebellectomy (closed arrow). These data are represented as described in fig. 4. NR = no response.

B. Histogram showing a comparison of the group data for pre- (to the left) and post- (to the right) cortical lesion stimulation (bar = 1 S.D.). Post-lesion threshold responses showed an increase in ipsilateral current intensities.


A
S8
S8
E6
W6
W6
W9
W13
W20
W7
E12
W6
E10
W6
W52
W8
E60
D8
NR
D8
NR
W10
NR
E6
E44
W6
NR
W6
NR
B
B
112PRE
112POS
5MM
4
3
2
1
0
5
4
3
2
1
-1

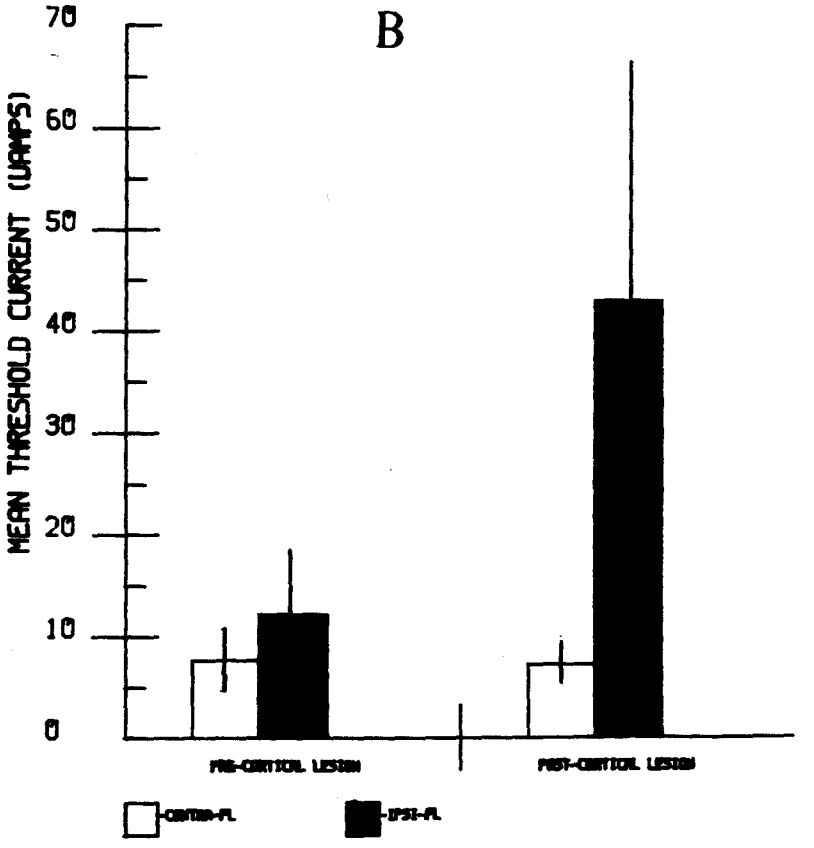
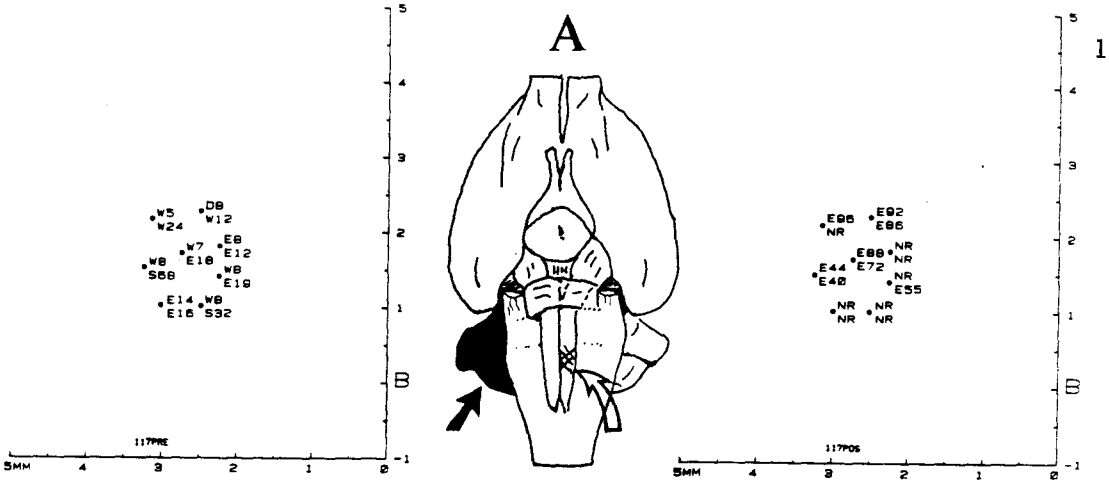

B
MEAN THRESHOLD CURRENT (UAMPS)
70
60
50
40
30
20
10
0
PRE-CORTICAL LESION
POST-CORTICAL LESION
CONTRA-PL
IPSI-PL

Figure 7.

A. Pre- (to the left) and post- (to the right) pyramidal lesion (open arrow) data from an animal (#117) that had sustained a neonatal hemicerebellectomy (closed arrow). These data are represented as described in fig. 4. NR = no response.

B. Histogram showing a comparison of the group data for pre- (to the left) and post- (to the right) pyramidal lesion stimulation (bar = 1 S.D.). Threshold current intensities were increased for both ipsi- and contra-lateral responses.


A
W5
W24
D8
W12
E8
E12
W7
E10
W8
S68
W8
E10
E14
E16
W8
S32
E96
NR
E92
E86
E88
NR
NR
E44
E72
NR
E40
E55
NR
NR
NR
NR
117PRE
117POS
5MM
4
3
2
1
0
-1
B

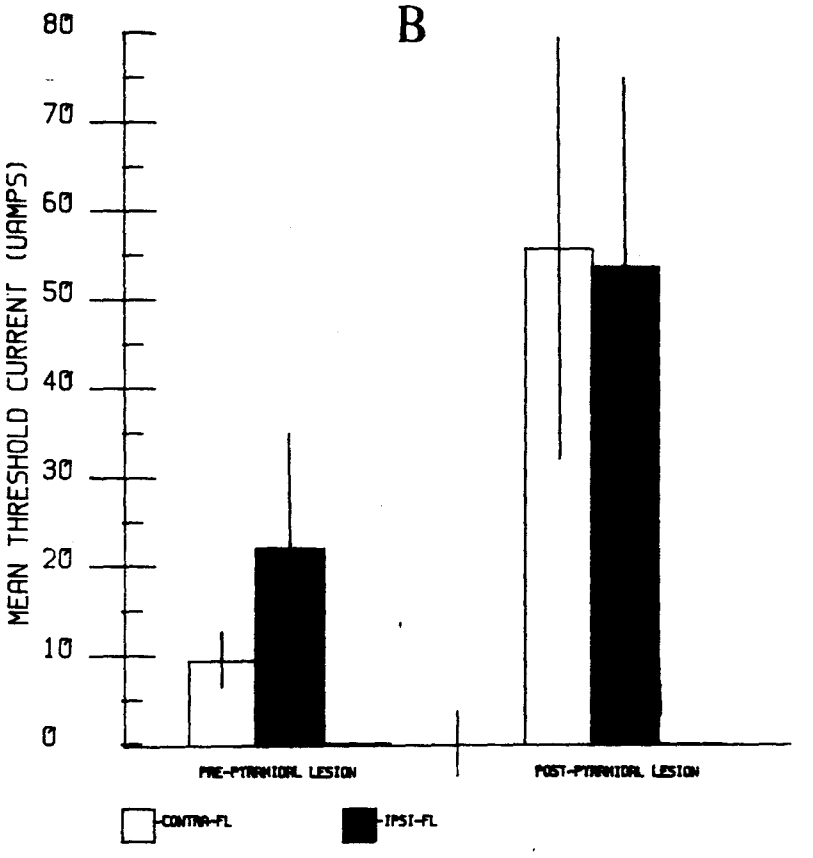
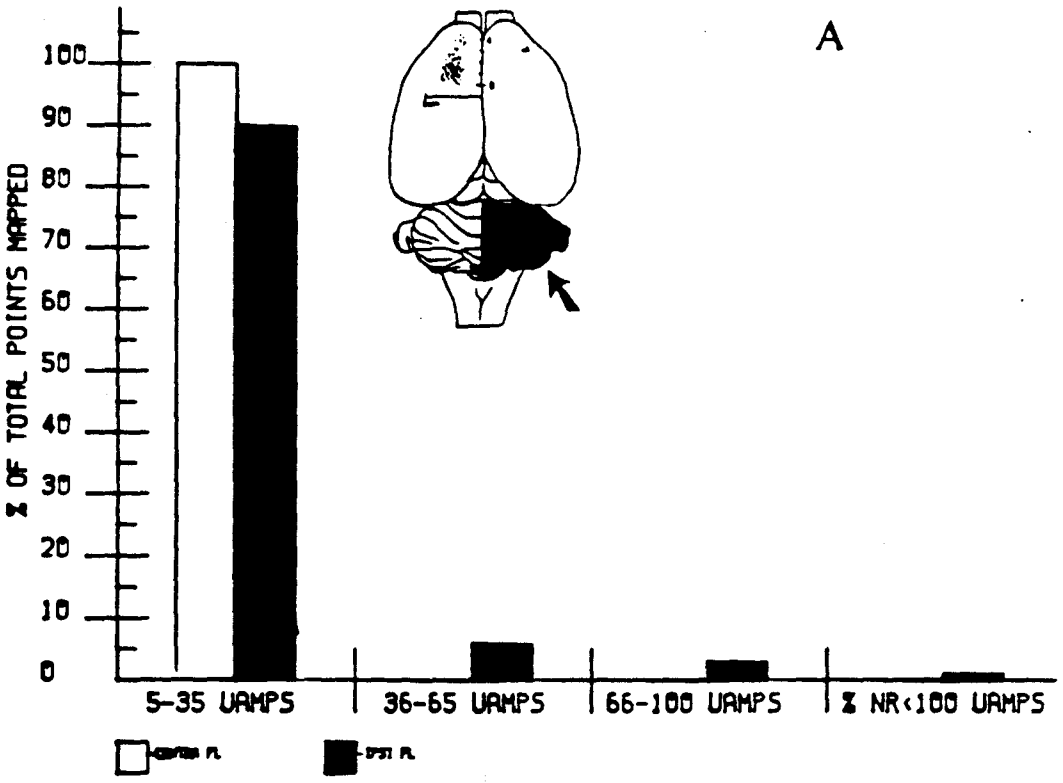

B
MEAN THRESHOLD CURRENT (UAMPS)
80
70
60
50
40
30
20
10
0
PRE-PTERYGOIDAL LESION
POST-PTERYGOIDAL LESION
CONTRA-FL
IPSI-FL

Figure 8.

A. Histogram of the distribution of threshold current values for contra- (open columns) and ipsi-lateral (black columns) forelimb responses in adult rats that had sustained either hemicerebellectomy (Expt. I, n=8) or total cerebellectomy (n=3) at 2 days of age. Arrow indicates neonatal lesion. Drawing indicates all electrode penetrations (dots) that evoked forelimb responses upon stimulation and is a composite of all animals used to demonstrate the distribution of threshold current values (only penetrations where contralateral respones were evoked below 35 uamps were considered in this distribution). Contralateral responses reflect our sampling bias. B = bregma; NR = no response.

B. Histogram of the distribution of threshold current values after ipsilateral pyramidal tract lesion (n=6) in adult animals that sustained a neonatal hemicerebellectomy (arrow). Note the shift (in comparison to A.) of threshold values to the right in these rats. Also note the large increase in % of no response.


A
100
90
80
70
60
50
40
30
20
10
0
% OF TOTAL POINTS MAPPED
5-35 UAMPS
36-65 UAMPS
66-100 UAMPS
% NR<100 UAMPS

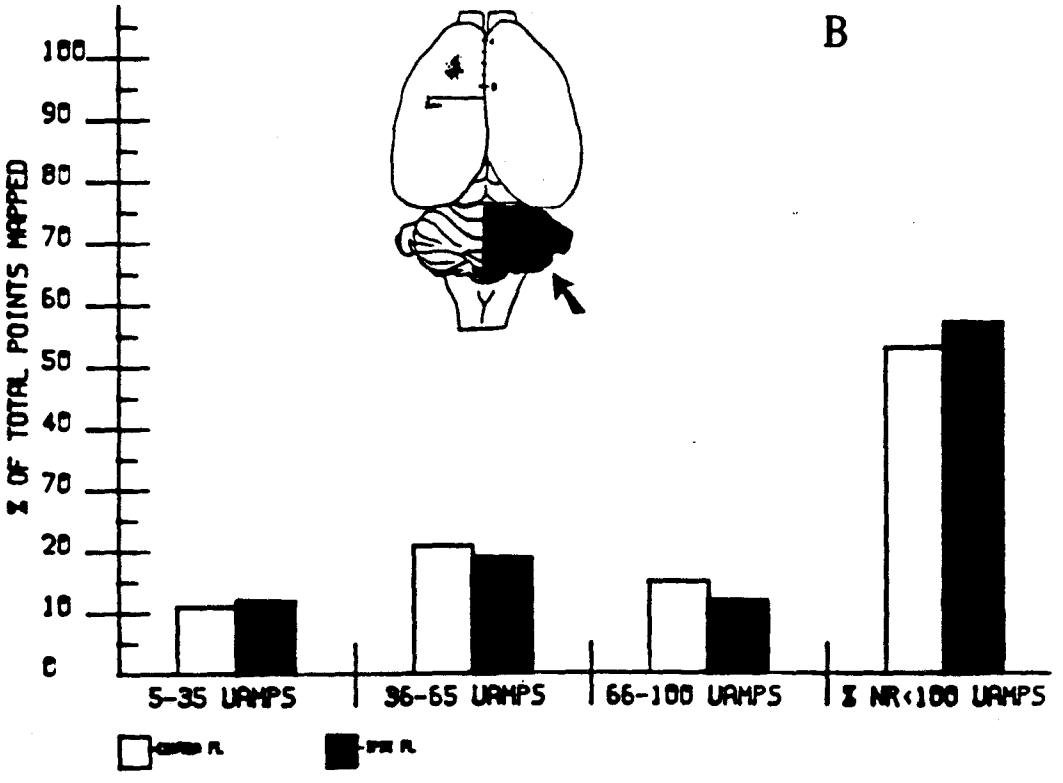
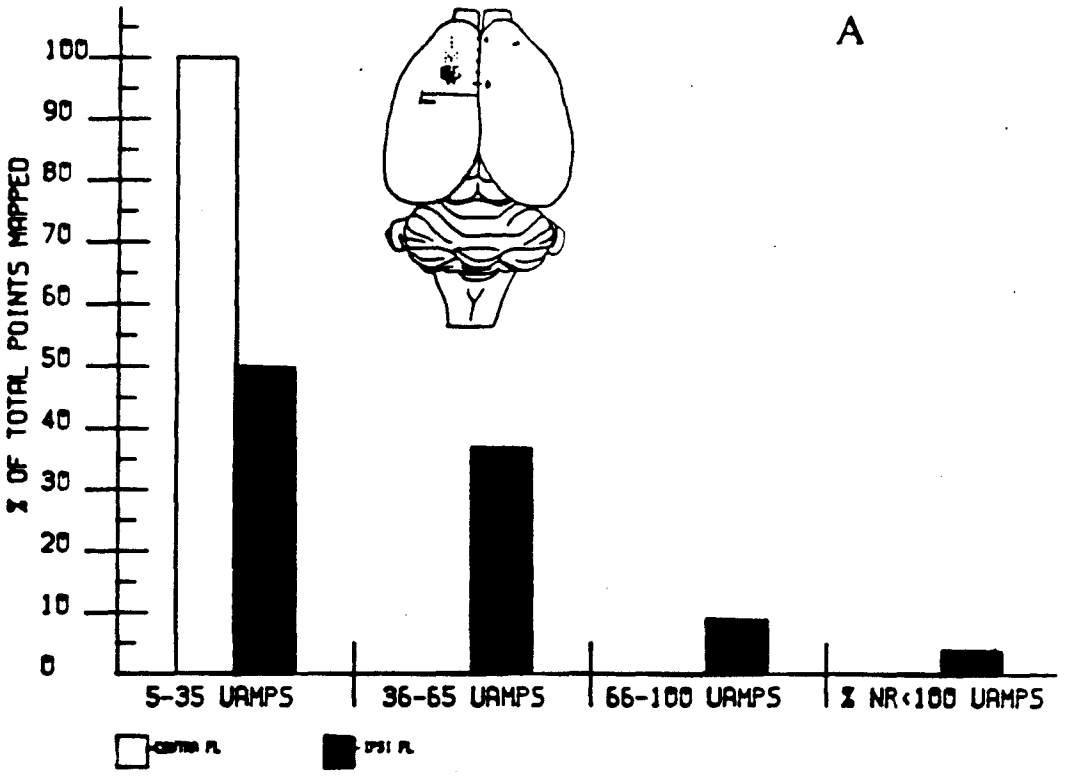

B
100
90
80
70
60
50
40
70
20
10
0
% OF TOTAL POINTS MAPPED
5-35 UAMPS
36-65 UAMPS
66-100 UAMPS
% NR<100 UAMPS

Figure 9.

A. Histogram of the distribution of threshold current values for contra- (open columns) and ipsi-lateral (black columns) forelimb responses in adult rats without neonatal lesion (Expt. I, n=7). Drawing indicates all electrode penetrations (dots) that evoked forelimb responses upon stimulation and is a composite of all animals used to demonstrate the distribution of threshold current values. B = bregma; NR = no response.

B. Histogram of the distribution of threshold current values for contra- (open column) and ipsi-lateral (black column) forelimb responses in adult animals (without neonatal lesions) with ipsilateral pyramidal tract lesions (n = 6). Drawing indicates location of all electrode penetrations (dots) where the results were compiled to show the distribution of threshold currents following pyramidal lesions.


A
100
90
80
70
60
50
40
30
20
10
0
% OF TOTAL POINTS MAPPED
5-35 UAMPS
36-65 UAMPS
66-100 UAMPS
% NR<100 UAMPS

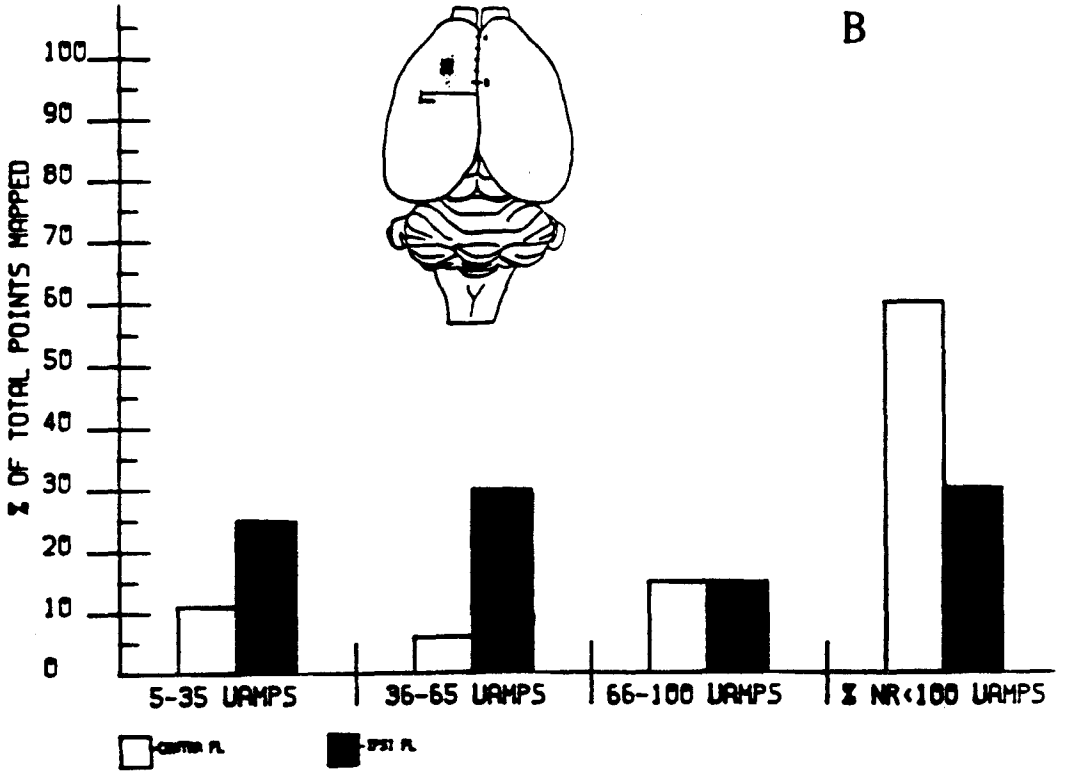
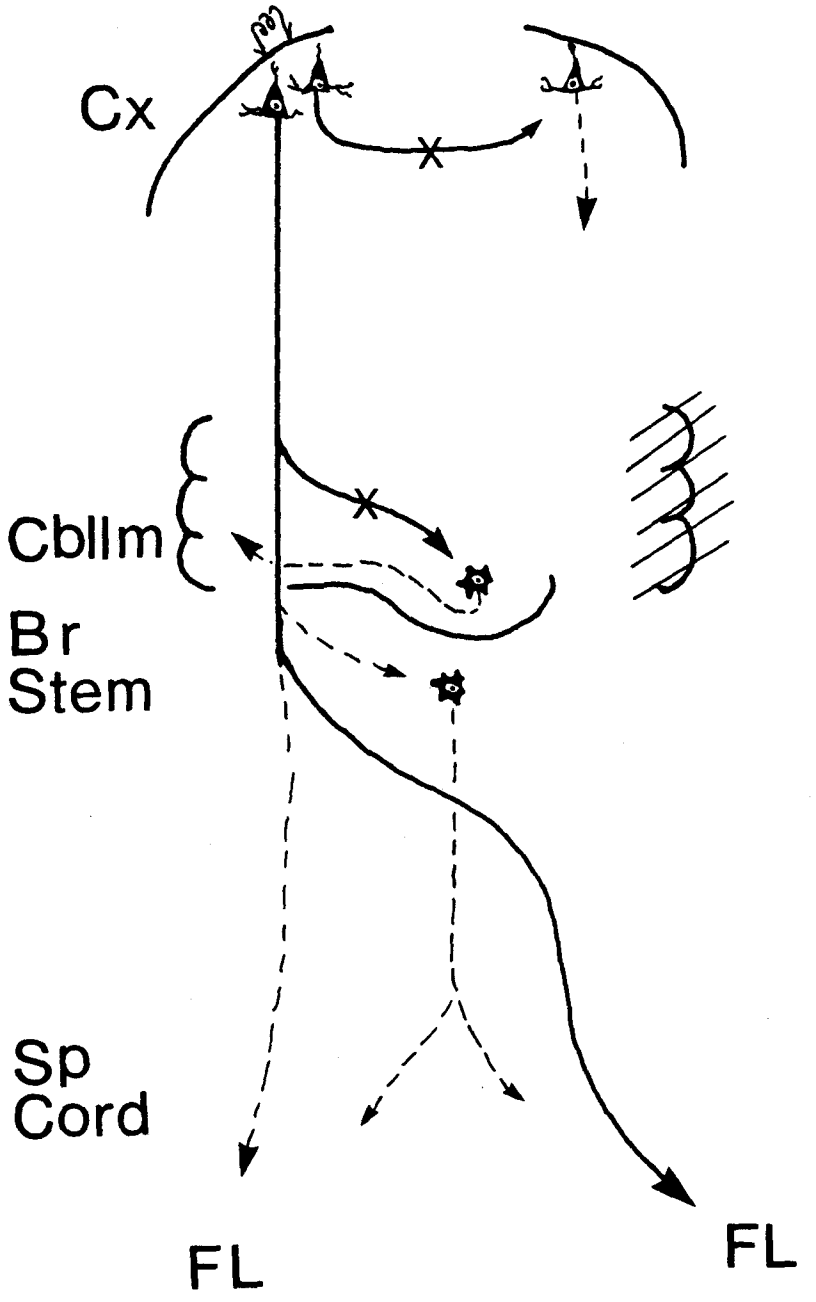

B
100
90
80
70
60
50
40
30
20
10
0
% OF TOTAL POINTS MAPPED
5-35 UAMPS
36-65 UAMPS
66-100 UAMPS
% NR<100 UAMPS

Figure 10. Summary diagram. X indicate pathways that play no role in the mediation of cortically-evoked forelimb responses (FL). Hatched area indicates the neonatal lesion; Cx = cortex; Cbllm = cerebellum; Br Stem = brain stem; Sp C = spinal cord.


Cx
Cbllm
Br
Stem
Sp
Cord
FL
FL

GENERAL DISCUSSION

Previous investigators found that recovery of postural and locomotor capabilities in rats that had sustained neonatal cerebellar lesions is more complete than that seen after cerebellar damage in older animals (Smith, et al., 1974a,b). Further behavioral studies (Smith et al., 1974b) examined the effects of secondary cortical lesions in adult rats that sustained cerebellar lesions at different neonatal ages and found that cortical lesions were more debilitating for those animals that had sustained cerebellar lesion at the youngest ages. These findings suggest that compensation for cerebellar damage involves the cerebral cortex, and that this involvement decreases when cerebellar lesions are incurred at older ages.

Intracortical microstimulation in adult rats (Expt. I) that had sustained cerebellar lesions at preweaning ages evoked ipsilateral forelimb movements at significantly reduced threshold current intensities when compared to animals that had sustained cerebellar lesions at older ages. These findings may in part provide electrophysiological support for the behavioral observations of a cortical role in compensation for cerebellar lesions in the young.

Smith and co-workers (1974b) postulated that neuroanatomical plasticity might explain the differences seen in compensation for cerebellar lesions sustained in the young when compared to adults.

This supposition was further strengthened by many subsequent reports that showed neuroanatomical remodelling in response to cerebellar lesions in the young (for review see Kawaguchi and Yamamoto, 1981). Also in response to neonatal cerebellar damage, cerebral cortical efferent projections have been shown to develope abberantly (Castro and Mihailoff, 1982; Expt. II)

Our anatomical studies (Expt. II) revealed corticopontine plasticity, in agreement with previous studies (Leong, 1977b, 1980; Castro and Mihailoff, 1982), and that alterations in cortico-midbrain projections may result from neonatal cerebellar lesions. However, no neuroanatomical remodelling of direct corticospinal projections was found which might explain abnormal ipsilateral threshold responses. In addition, no aberrant cortico-bulbar projections to cell groups that might influence the ipsilateral spinal cord were found. Secondary lesion studies indicated that callosal or cerebellar connections do not mediate low threshold ipsilateral responses. Although secondary cortical lesions did effect threshold currents for ipsilateral responses evoked from the intact cortex, this was apparently an indirect result of spinal disfascilitation. Lesions of the medullary pyramid had a marked effect on the threshold currents of both ipsilateral and contralateral forelimb responses indicating that the pyramidal tract mediates low-threshold responses observed upon stimulation of the cerebral cortex (Expt. III, see also fig. 1).

The possibility remains that the abnormal responses are mediated

by alterations at spinal cord levels. Retrograde cellular changes in Clarke's column (nucleus dorsalis) have been reported after neonatal hemicerebellectomy (Smith and Castro, 1979); the extent of these changes was dependent upon the age of the animal at the time of cerebellar lesion. Neonatal hemicerebellectomy also causes alterations in ascending spinal projections to vestibular nuclei and to the cerebellum (Castro and Hazlett, 1979; Castro and Smith, 1979). Although these observations of changes within the spinal cord may not be related to abnormal threshold responses, these data indicate that there are alterations in the spinal cord after cerebellar lesions and that the extent of changes depends upon the age of animal at the time of lesion.

The differences in functional recovery seen after cerebellar lesions may also reflect a differential effect upon the spinal cord of age at time of lesion. Cerebellar lesions in adults have a depressive effect on spinal cord activity (Granit, 1977) resulting in the classic symptoms of hypotonia and asthenia (Holmes, 1922; 1939; Chambers and Sprague, 1955; Crosby, et al., 1966; Eccles, 1977; Stenvers, et al., 1983). Furthemore, adult cerebellar ablated animals have delayed reaction times and are generally slow and clumsy during ambulation (Smith, et al., 1974a, personal observation). By contrast, neonatal cerebellar operates are active and coordinated (Smith, et al., 1974b). The extent of recovery is such that by casual observation it is difficult to tell many of these animals apart from non-lesion adults

(Leong, 1977a; personal observation). Based upon these behavioral observations, neonatal hemicerebellectomy does not seem to result in the same depressive effects on spinal cord activity as do similar lesions in adult animals.

The baseline activity in the spinal cord may be important for evaluating threshold currents for cortically evoked responses. Spinal interneurons that mediate multisynaptic corticospinal effects receive other afferent systems as well, i.e. dorsal root, propriospinal and other descending pathways (for review see Baldissera, et al., 1981). An increase in the activity of any one of these systems can cause a decrease in the threshold for responses observed through the other projections (Lloyd, 1941; Lundberg and Voorhoeve, 1962; Lundberg, 1975; Illert, et al., 1976a,b; 1977). The significant decrease in current thresholds which elicit ipsilateral forelimb movements after neonatal hemicerbellectomy may reflect an increase in the activity of spinal or brainstem circuits (see fig. 2) and not an alteration of the corticospinal tract per se (see Expt II).

The elevation of current thresholds needed to evoke limb movements after a medullary pyramidotomy in monkeys (Woolsey, et al., 1972), dogs (Gorska, et al., 1980), cats (Nieoullin and Cahery, 1978; Asanuma, et al., 1981), and rats (Barron, 1934; Expt. III), indicates the involvement of corticospinal fibers in low-threshold, cortically-evoked movements (for review see Asanuma, 1981). The rodent corticospinal tract has generally been regarded as a completely crossed

pathway (King, 1910; Dunkerley and Duncan, 1969; Brown, 1971), but some anatomical studies demonstrate a small ipsilateral component (Goodman, et al., 1966; Vahlsing and Feringa, 1980). In the rat, corticospinal fibers activate spinal motorneurons mono- and multisynaptically and thereby mediate the forelimb movements evoked in cortical stimulation studies (Elger, et al., 1977). The low threshold currents needed to evoke contralateral movements in normal animals, when compared to threshold currents for ipsilateral responses, probably reflects the predominantly crossed termination of the corticospinal tract acting upon a certain baseline of activity.

The neonatal cerebellar-lesion-induced increase in postural tone (Smith, et al., 1974a,b; Gramsbergen, 1981) may reflect an increase in the baseline activity of the spinal interneuronal pool. With an increased baseline activity that may occur after cerebellar lesions in the young (a hypertonic reflex state), cortically applied currents evoke movements at lowered threshold values, as was demonstrated for ipsilateral movements (Expt. I). One might expect similar changes for contralateral responses. While the differences observed were not large, a slight lowering of threshold currents for contralateral movements was found in animals sustaining cerebellar lesions at young ages (see Expt I). In comparison, cerebellar lesions at maturity, which are generally regarded to cause hypotonicity (for review see Eccles, 1977), might be associated with an increase in threshold current values. However, no real increase was found (Expt. I). From

the hypothesis based on alterations in postural tone after cerebellar lesions, our data are interpreted in terms of an increase in the spinal cord's responsiveness to cortically applied stimulation. Further work would be necessary to verify if spinal reflex pathways in neonatal operates were substantially different than control animals.

The behavioral mechanisms of functional recovery from cerebellar lesion may depend upon the age of the animal at the time of the lesion. Following neonatal lesions, the animals have no discernible deficits for a matter of weeks (Dow and Moruzzi, 1958; Smith, et al., 1974b; Gramsbergen, 1981). With maturity, they learn to ambulate and function in the absence of some cerebellar tissue. By contrast, normal animals develop definite patterns of movements for accomplishing intended behaviors. Following the adult lesion, these animals show an immediate deficit. Secondary effects include atrophic changes in muscle tissue (Stenvers, et al., 1983) resulting in further behavioral deficits. Previous patterns of motor behaviors are inadequate to overcome the deficit-imposed restrictions. Those behaviors once directed through lower brainstem areas that carried out intended activity in an almost automatic fashion are lost. The neonatal operates have no such restrictions. They accomplish motor activity without having to override a previous mode of operation. With the cerebral motor cortex able to direct discrete limb movements (Kuypers, 1982), compensation for neonatal cerebellar lesions may proceed along the "pathway of least resistance" (Smith, et al., 1974b). Although our studies indicate that

the redirection of growing axons is not responsible for the abnormal thresholds observed, possibly more subtle changes in spinal cord synaptology occur as a consequence of the increased importance of the cerebral cortex after cerebellar lesions in the young.

Figure 1. Diagramatic representation of corticospinal influences on ipsi- and contra-lateral motoneurons. Broken line indicates sparce ipsilateral corticospinal projection, while the solid line indicates the prominent contralateral projection.

A. Normal animal

B. Projections after neonatal hemicerebellectomy (arrow). Apparently normal tracts have altered influence.

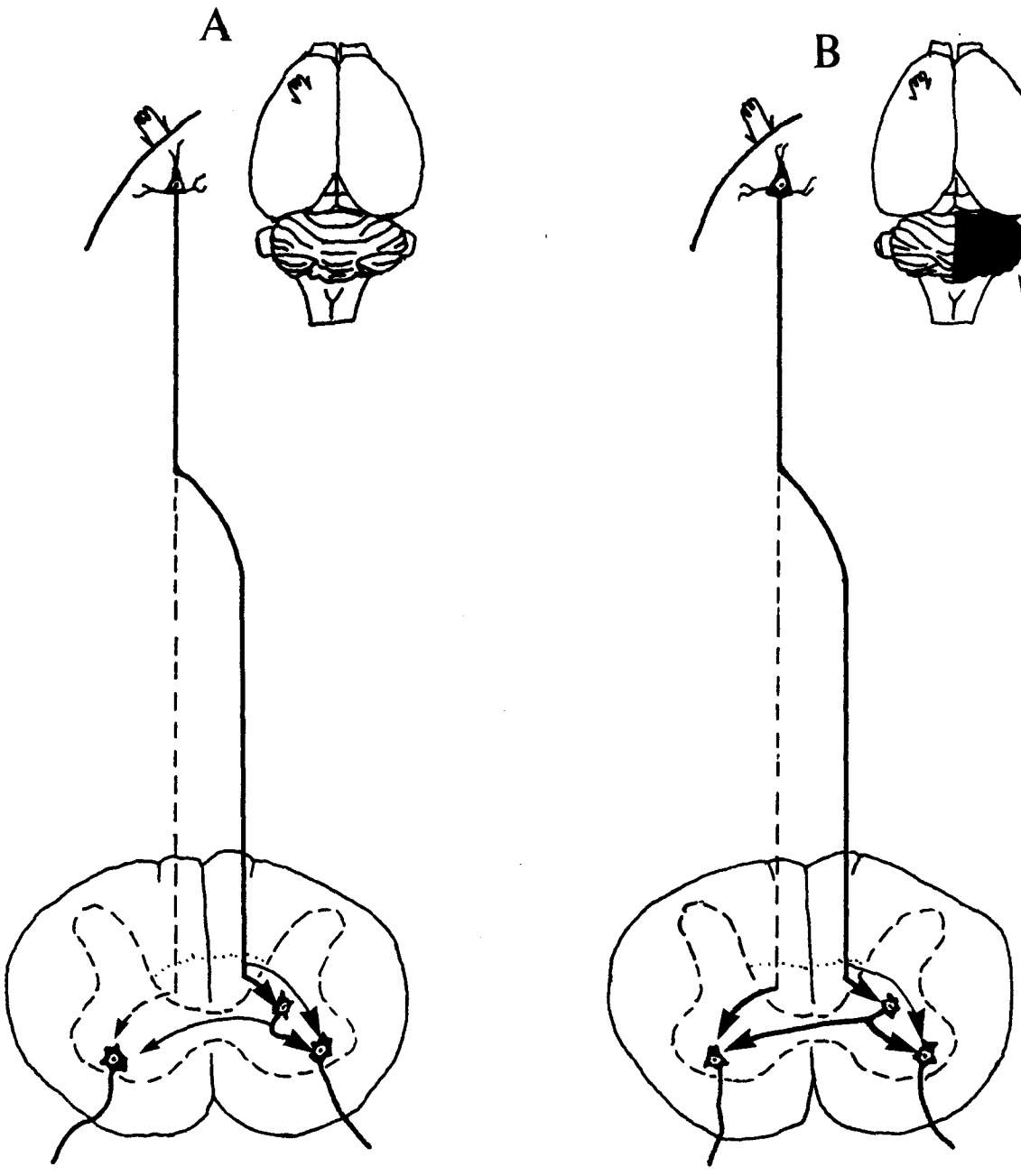
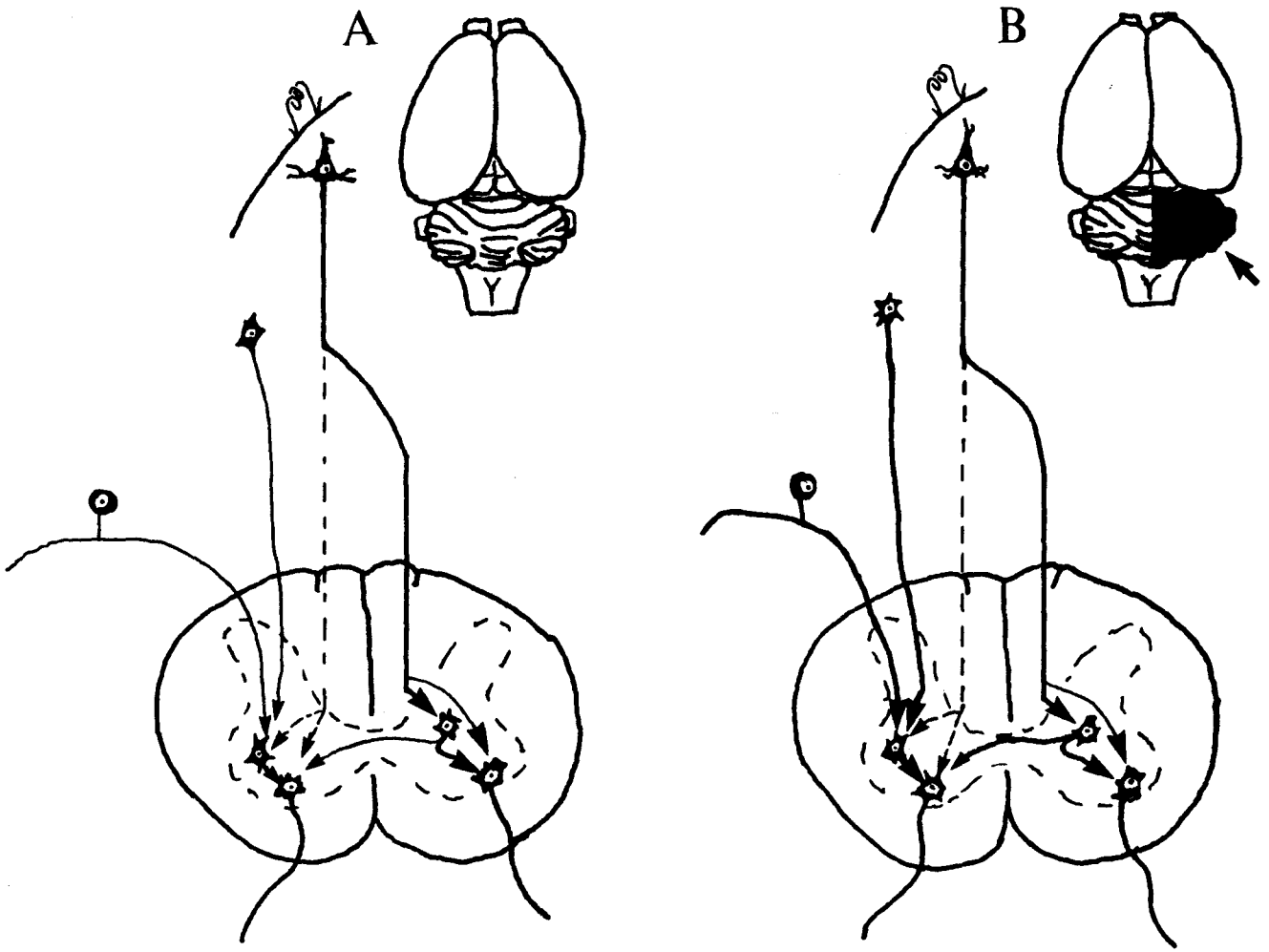

A
B

Figure 2.

A. Normal animal. Diagram indicating the convergence of descending brainstem and dorsal root fibers with corticospinal projections upon spinal interneurons which in turn relay to alpha motoneurons.

B. After neonatal hemicerebellectomy an increase in activity of either descending brainstem or dorsal root fibers would result in lowered threshold for cortically evoked responses.


A
B

SUMMARY

Neuroanatomical plasticity is defined as the development of anomalous neuronal connections in resonse to central nervous system injury. Previous reports have described the formation of aberrant projections after cerebellar lesions in newborn rats. Additionally, behavioral studies have shown that the dysfunctions associated with cerebellar lesions are less severe after lesions in the young when compared to similar lesions in older animals and that the cerebral cortex may be important for recovery seen only after neonatal lesions (Smith et al., 1974a, 1974b). The correlation of neuroanatomical plasticity and cerebral cortical participation in functional recovery suggests that cerebellar lesions cause alterations in cortical projections that may account for behavioral observations.

Although subsequent anatomical studies did show the formation of anomalous corticopontine projections after cerebellar lesions in young rats (Castro and Mihailoff, 1982), the relationship between functional recovery and neuroanatomical plasticity remains unclear. The experiments of this dissertation were designed to examine (both electrophysiologically and anatomically) cerebral motor cortical efferents after cerebellar lesions at various ages.

In normal adult rats, microstimulation of the motor cortex evokes low-threshold contralateral and high-threshold ipsilateral

forelimb movements. These responses are apparently mediated by the corticospinal tract which has predominantly crossed and sparse uncrossed terminations. If neonatal cerebellar lesions substantially alter motor cortical projections then intracortical microstimulation should reveal abnormal evoked responses. Such a correlation has been suggested by studies in animals after neonatal cortical lesions (Kartje-Tillotson, et al., 1984).

The first studies were designed to examine limb movements evoked by microstimulation of the cerebral cortex in rats that had sustained hemicerebellectomy at various ages. In animals ablated prior to weaning, ipsilateral movements were evoked at significantly lower threshold current intensities in comparison to those needed to elicit similar movements after cerebellar lesions at older ages or in normal control animals. These results suggest that neonatal hemicerebellectomy might induce the formation of aberrant corticospinal projections, or alternatively aberrant corticobulbar projections to areas that in turn project to the spinal cord.

In search of the neuroanatomical basis for the abnormal, low-threshold, ipsilateral forelimb movements, the second studies were undertaken to examine alterations in motor cortical projections which may develop after neonatal hemicerebellectomy. Injections of horseradish peroxidase were made into low-threshold forelimb cortical areas and the distribution of cortical efferent projections was traced to the brainstem and spinal cord. No neuroanatomical remodelling of

direct corticospinal projections or aberrant corticobulbar projections to cell groups that might influence the ipsilateral spinal cord was found.

Since corticospinal remodelling was not observed, the last experiments were designed to determine which neural structures may contribute to or mediate the low-threshold, ipsilateral, forelimb movements observed after neonatal hemicerebellectomy. Adult animals that had sustained neonatal cerebellar lesions received only one of four secondary lesions. Different animals received lesions of cerebellar tissue spared by the neonatal lesion, the corpus callosum, the opposite cerebral hemisphere or the medullary pyramid. Following these lesions, intracortical microstimulation showed that secondary cerebellar or callosal lesions did not abolish the abnormal, low-threshold, ipsilateral forelimb movements evoked by intracortical stimulation. Thus, the contralateral cerebral cortex or spared cerebellum do not seem to mediate low-threshold responses. Secondary cortical lesions, although they caused a marked increase in the threshold currents for ipsilateral forelimb responses, effect cortically-evoked responses only indirectly. Pyramidal lesions increased the threshold currents needed to elicit ipsilateral, as well as contralateral, forelimb movements. This indicates that normal and abnormal low-threshold, cortically-evoked, forelimb responses are mediated by the corticospinal tract.

The lack of corticospinal as well as corticobulbar plasticity

that might correspond to the observed low-threshold ipsilateral forelimb movements suggests that these responses are mediated via normal corticospinal fibers. Possibly, alterations at spinal cord levels may occur in response to neonatal cerebellar lesions and therefore explain the low-threshold ipsilateral forelimb movements evoked by intracortical microstimulation.

BIBLIOGRAPHY

Allen, G.I. and N. Tsukahara, 1974. Cerebrocerebellar communication systems. Pysiological Rev., 54: 957-1006.

Altman, J., 1982. Morphological development of the rat cerebellum and some of its mechanisms, In: S.L. Palay and V. Chan-Palay, Eds., The Cerebellum: New Vistas. Springer-Verlag, New York, pp. 8-49.

Altman, J. and K. Sudarshan, 1975. Postnatal development of locomotion in the laboratory rat. Animal Behav., 23: 896-920.

Angel, A. and R.N. Lemon, 1975. Sensorimotor cortical representation in the rat and the role of the cortex in the production of sensory myoclonic jerks. J. Physiol., 248: 465-488.

Armand, J., 1982. The origin, course and terminations of corticospinal fibers in various mammals. Prog. in Brain Res., 57: 330-360.

Armand, J. and R. Aurenty, 1977. Dual organization of motor corticospinal tract in the cat. Neurosci. Letters, 6: 1-7.

Armand, J. and H.G.J.M. Kuypers, 1980. Cells of origin of crossed and uncrossed corticospinal fibers in the cat. Exp. Brain Res., 40: 23-34.

Asanuma, H., 1981. The pyramidal tract, In: J.M. Brookhart and V.B. Mountcastle, Eds., Handbook of Physiology - The Nervous System II, Williams and Wilkens Co. Baltimore, pp. 703-733.

Asanuma, H., A. Arnold and P. Zarzecki, 1976. Further study on the excitation of pyramidal tract cells by intracortical microstimulation. Exp. Brain Res., 26: 443-461.

Asanuma, H. and J.J. Fernandez, 1974. Organization of projection from the thalamic relay nuclei to the motor cortex in the cat. Brain Res., 71: 515-522.

Asanuma, H. and R. Hunsperger, 1975. Functional significance of projection from the cerebellar nuclei to the motor cortex in the cat. Brain Res., 98: 73-92.

Bach-y-Rita, P., 1981. Central nervous system lesions: Sprouting and unmasking in rehabilitation. Arch. Phys. Med. Rehabil., 62: 413-417.

Baldissera, F., H. Hultborn, and M. Illert, 1981. Intergration in

spinal neuronal systems, In: J.M. Brookhart and V.B. Mountcastle, Eds., Handbook of Physiology - The Nervous System II, Williams and Wilkens Co., Baltimore, pp. 509-595.

Bantli, H. and J.R. Bloedel, 1976. Characteristics of the output from the dentate nucleus to spinal neurons via pathways which do not involve the primary sensorimotor cortex. Exp. Brain Res., 25: 199-220.

Barnes, C. D. and J. Schadt, 1979. Release of function in the spinal cord. Prog. in Neurobiol., 12: 1-13.

Barron, D.H., 1934. The results of unilateral pyramidal section in the rat. J. of Comp. Neur., 60: 45-56.

Basbaum, A.I., C. Clanton and H.L. Fields, 1978. Three bulbospinal pathways from the rostral medulla of the cat: An autoradiographic study of pain modulating systems. J. of Comp. Neur., 178: 209-224.

Bentivoglio, M. and H.G.J.M. Kuypers, 1982. Divergent axon collaterals from rat cerebellar nuclei to diencephalon, mesencephalon, medulla oblongata and cervical cord. Exp. Brain Res., 46: 339-356.

Biber, M.P., L.M. Kneisley and J.H. LaVail, 1978. Cortical neurons projecting to the cervical and lumbar enlargements of the spinal cord in young and adult monkeys. Exp. Neurol., 59: 492-508.

Biedenbach, M.A. and J.L.Devito, 1980. Origin of the pyramidal tract determined with horseradish peroxidase. Brain Res., 193: 1-17.

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

Brodal, P., 1982. The cerebropontocerebellar pathway: Salient features of its organization, In: S.L. Palay and V. Chan-Palay, Eds., The Cerebellum: New Vistas. Springer-Verlag, New York, pp. 108-133.

Bower, J.M., D.H. Beermann, J.M. Gibson, G.M. Shambes and W. Welker, 1981. Principles of organization of a cerebro-cerebellar circuit. Brain Behav. 18: 1-18.

Brooks, V.B. and W.T. Thach, 1981. Cerebellar control of posture and movement, In: J.M. Brookhart and V.B. Mountcastle, Eds., Handbook of Physiology - The Nervous System II. Williams and Wilkens Co., Baltimore, pp. 877-946.

Brown, L.T., 1971. Projections of the corticospinal tract in rodents. Exp. Brain Res., 13: 432-450.

Brown. L.T., 1974. Corticorubral projections in the rat. J. of Comp Neur., 154: 149-168.

Brown, L.T., 1974. Rubrospinal projections in the rat. J. of Comp Neur., 154: 169-188.

Burgess, J.W., J. R. Villablanca, C.E. Olmstead, and M.S. Levine, 1982. Differential recovery from hemispherectomy in kittens and cats. Neurosci. abstr. 8: 746.

Burne, R.A., M.A. Eriksson, J.A. Saint-Cyr and D.J. Woodward, 1978. The organization of the pontine projection to lateral cerebellar areas in the rat: Dual zones in the pons. Brain Res., 139: 340-347.

Castro, A.J., 1972. Motor performance in rats. The effects of pyramidal tract section. Brain Res., 44: 313-323.

Castro, A.J., 1972. The effects of cortical ablations on digital usage in the rat. Brain Res., 37: 173-185.

Castro, A.J., 1975. Ipsilateral corticospinal projections after a large lesion of the cerebral hemisphere in neonatal rats. Exp. Neur., 46: 1-8.

Castro, A.J., 1977. Limb preference after lesions of the cerebral hemisphere in adult and neonatal rats. Physiol. and Behav., 18: 605-608.

Castro, A.J., 1978. Projections of the superior cerebellar peduncle in rats and the development of new connections in response to neonatal hemicerebellectomy. J. of Comp. Neur., 178: 611-628.

Castro, A. and J.C. Hazlett, 1979. Spinocerebellar sprouting in response to neonatal hemicerebellectomy. Anat. Rec., 193: 501-502A.

Castro, A. and D.E. Smith, 1979. Plasticity of spinovestibular projections in response to hemicerebellectomy in newborn rats. Neurosci. Letters, 12: 69-74.

Castro, A.J. and G.A. Mihailoff, 1982. Corticopontine remodelling after cortical and/or cerebellar lesions in newborn rats. J. Comp. Neur., 219: 112-123.

Castro, A.J., G. Kartje-Tillotson, D. Barnes, D. O'Donoghue, and R. Swenson, 1984. The effects of neonatal 6-OHDA treatment on motor cortical plasticity. A study of forelimb movements evoked by intracortical microstimulation. Neurosci. Letters, Abstract in press.

Catsman-Berrevoets, C.E., H.G.J.M. Kuypers and R.N. Lemon, 1979. Cells of origin of the frontal projections to magnocellular and parvocellular red nucleus and superior colliculus in cynomolgus monkey. An HRP study. Neurosci. Letters, 12: 41-46.

Catsman-Berrevoets, C.E., R.N. Lemon, C.A. Berburgh, M. Bentivoglio and H.G.J.M. Kuypers, 1980. Absence of callosal collaterals derived from rat corticospinal neurons. Exp. Brain Res., 39: 433-440.

Chambers, W.W. and J. M. Sprague, 1955. Functional localization in the cerebellum I. Organization in longitudinal cortico-nuclear xones and their contribution to the control of posture, both extrapyramidal and pyramidal. J. of Comp. Neur., 103: 105-129.

Cospito, J.A. and K. Kultas-Ilinsky, 1981. Synaptic organization of motor corticostriatal projections in the rat. Exp. Neur., 72: 257-266.

Corvaja, N. and O. Pompeiano, 1979. Identification of cerebellar corticovestibular neurons retrogradely labeled with horseradish peroxidase. Neurosc., 4: 507-515.

Cotman, C.E., 1978. Neuronal Plasticity. Raven Press, New York.

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

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

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

Crosby, E.C., R.C. Schneider, B.R. DeJonge and P. Szonyi, 1966. The alterations of tonus and movements through the interplay between the cerebral hemispheres and the cerebellum. J. of Comp. Neur., 127: 1-91.

Dekker, J.J., 1981. Anatomical evidence for direct fiber projections

from the cerebellar nucleus interpositus to rubrospinal neurons. A quanitative EM study in the rat combining anterograde and retrograde intra-axonal tracing methods. Brain Res., 205: 229-244.

Dodds, W.J., 1878a. On the localization of the functions of the brain: Being an historical and critical analysis of the question: Historical sketch. J. Anat. and Physiol., 12: 340-363.

Dodds, W.J., 1878b. On the localization of the functions of the brain: Being an historical and critical analysis of the question: Physiological. J. Anat. and Physiol., 12: 455-494.

Donatelle, J.M., 1977. Growth of the corticospinal tract and the development of placing reactions in the postnatal rat. J. of Comp. Neur., 175: 207-232.

Donoghue, J.P., K. Kerman and E.F. Ebner, 1979. Evidence for two organizational plans within the somatic sensory-motor of the rat. J. of Comp. Neur., 183: 647-664.

Donoghue, J.P. and C. Parham, 1983. Afferent connections of the lateral agranular field of the rat motor cortex. J. of Comp. Neur., 217: 390-404.

Donoghue, J.P. and S. Wise, 1982. The motor cortex of the rat: Cytoarchitecture and microstimulation mapping. J. of Comp Neur., 212: 76-88.

Dow, R.S. and Moruzzi G., 1958. The Physiology and Pathology of the Cerebellum. Minneapolis, Univ. of Minnesota Press.

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

Eccles, J., 1977. Cerebellar function in the control of movement, In: F.C. Rose, Ed., Physiological Aspects of Clinicial Neurology, Blackwell Scientific Publications, Oxford, pp. 157-178.

Eccles, J.C., N.J. Sabah, R.F. Schmidt and J. Taborikova, 1972. Mode of operation of the cerebellum in the dynamic loop control of movement. Brain Res., 40: 73-80.

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

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

Everts, E.V., 1981. Role of motor cortex in volentary movements in primates, In: J.M. Brookhart and V.B. Mountcastle, Eds., Handbook of Physiology: The Nervous System II, Williams and Wilkens Co., Baltimore, pp. 1083-1120.

Faull, R.L. and J.B. Carman, 1978. The cerebellofugal projections in the brachium conjunctivum of the rat. I. The contralateral ascending pathway. J. of Comp. Neur., 178: 495-518.

Faull, R.L., 1978. The cerebellofugal projections in the brachium conjunctivum of the rat. II. The ipsilateral and contralateral descending pathways. J. of Comp. Neur., 178: 519-536.

Ferrier, D., 1873. Experimental researches in cerebral physiology and pathology. W. Riding Lunatics Asylum Med. Rep., 3: 30-96.

Finger, S. and D.G. Stein, 1982. Brain Damage and Recovery, Research and Clinical Perspectives, Academic Press, Inc., New York.

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

Gilman, S. and L. Marco, 1971. Effects of medullary pyramidotomy in the monkey. I. Clinical and electromyographic abnormalities. Brain, 94: 495-514.

Gilman, S., L.A. Marco, and H.C. Ebel, 1971. Effects of medullary pyramidotomy in the monkey. II. Abnormalities of spindle afferent responses. Brain, 94: 515-530.

Gilman, S., J.S. Lieberman, and L.A. Marco, 1974. Spinal mechanisms underlying the effects of unilateral ablation of areas 4 and 6 in monkeys. Brain, 97: 49-64.

Giuffrida, R., F. Licata, G. Li Volsi, and V. Perciavalle, 1982. Motor responses evoked by microstimulation of cerebellar interpositus nucleus in cats submitted to dorsal rhizotomy. Neurosci. Letters, 30: 241-244.

Goldberger, M.E., 1980. Motor recovery afte r lesions. Trends in Neurosci., 3: 288-291.

Goldberger, M.E., 1981. The role sprouting might play during the recovery of motor functions. In: H. Flohr and W. Precht, Eds., Lesion-Induced Neuronal Plasticity in Sensorimotor Systems,

Springer-Verlag, New York, 130-140.

Goldman, P., 1974. 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, 149-174.

Goldman, P. and T. Galkin, 1978. Prenatal removal of frontal association cortex in the fetal rhesus monkey: Anatomical and functional consequences in postnatal life, Brain Res., 152: 451-485.

Goodman, D.C., E. Jarrard and J.F. Nelsen, 1966. Corticospinal pathways and their sites of termination in the albino rat. Anat. Rec., 154: 462.

Gorska, T., C. Woolsey and A. Wetzel, 1980. Motor effects of cortical stimulation after chronic lesion of medullary pyramid in the dog. Neurobiol. Exp., 40: 861-879.

Gramsbergen, A., 1981. Locomotor behavior after lesions in the young rat. In: Lesion-Induced Neuronal Plasticity In Sensorimotor Systems. ed. H. Flohr and W. Precht, Springer-Verlag, New York.

Gramsbergen, A. and J. Ijkma-Paassen, 1982. CNS plasticity after hemicerebellectomy in the young rat. Quantitative relations between aberrant and normal cerebello-rubral projections. Neurosci. Letters, 33: 129-133.

Granit, R., 1977. Reconsidering the 'alpha-gamma' switch in cerebellar action, In: F.C. Rose, Ed., Physiological Aspects of Clinical Neurology, Blackwell Scientific Publications, Oxford, pp. 201-214.

Granit, R., B. Holmgren and P.A. Merton, 1955. The two routes for excitation of muscle and their subservience to the cerebellum. J. Physiol., 130: 213:224.

Groos, W.P., L.K. Ewing, C.M. Carter and J. Coulter, 1978. Organization of corticospinal neurons in the cat. Brain Res., 143: 393-419.

Gwyn, D.G. and B.A. Flumerfelt, 1974. A comparison of the distribution of cortical and cerebellar afferents in the red nucleus of the rat. Brain Res., 69: 130-135.

Haines, D.E., G.W. Patrick and P. Satrulee, 1982. Organization of cerebellar corticonuclear fiber systems. In: S.L. Palay and V.

Chan-Palay, Eds., The Cerebellum: New Vistas. Springer-Verlag, New York, pp. 320-371.

Hall, R.D. and E.P. Lindholm, 1974. Organization of motor and somatosensory neocortex in the albino rat. Brain Res., 66: 23- 38.

Haroian, A.J., L.C. Massopust, and P.A. Young, 1981. Cerebellothalamic projections in the rat: An autoradiographic and degeneration study. J. of Comp. Neur., 197: 217-236.

Hayes, N.L. and A. Rustioni, 1981. Descending projections from brainstem and sensorimotor cortex to spinal enlargements in the cat. Exp. Brain Res., 41: 89-107.

Heffner, R., and B. Masterton, 1975. Variation in form of the pyramidal tract and its relationship to digital dexterity. Brain Beh., 12:161-200.

Hicks, S.P. and C.J. D'Amato, 1970. Motor-Sensory and visual behavior after hemispherectomy in newborn and adult rats. Exp. Neurol., 29: 416-438.

Hicks, S.P. and C. J. D'Amato, 1975. Motor-sensory cortex-cortico spinal system and developing locomotion and placing in rats. Am. J. of Anat., 143: 1-42.

Hicks, S.P. and C.J. D'Amato, 1977. Locating corticospinal neurons by retrograde axonal transport of horseradish peroxidase. Exp. Neur., 56: 410-420.

Holmes, G., 1922. The Croonian lectures on the clinical symptons of cerebellar diseases and their interpretation. Lancet, 100: 1231-1237.

Holmes, G., 1939. The cerebellar of man. Brain, 62: 1-30.

Huisman, A.M., H.G.J.M. Kuypers and C.A. Verburgh, 1981. Quantitative differences in collateralization of the descending spinal pathways from red nucleus and other brain stem cell groups in rat as demonstrated with the multiple fluorescent retrograde tracer technique. Brain Res., 209: 271-286.

Huisman, A.M., H.G.J.M. Kuypers and C.A. Verburgh, 1982. Differences in collateralization of the descending spinal pathways from red nucleus and other brain stem cell groups in cat and monkey. Prog. in Brain Res., 57: 185-217.

Huisman, A.M., H.G.J.M. Kuypers, F. Conde and K. Keizer, 1983.

Collaterals of rubrospinal neurons to the cerebellum in rat: A retrograde fluorescent double labeling study. Brain Res., 264: 181-196.

Illert, M., A. Lundberg and R. Tanaka, 1976a. Integration in descending motor pathways controlling the forelimb of the cat. I. Pyramidal effects on motoneurones. Exp. Brain Res., 26: 509-519.

Illert, M., A. Lundberg and R. Tanaka, 1976b. Integration in descending motor pathways controlling the forelimb in the cat. II. Convergence on neurones mediating disynaptic cortico-motoneuronal excitation. Exp. Brain Res., 26: 521-540.

Illert, M., A. Lundberg and R. Tanaka, 1977. Intergration in descending motor pathways controlling the forelimb in the cat. III. Convergence on propriospinal neurones transmitting disynaptic excitation from the corticospinal trace and other descending tracts. Exp. Brain Res., 29: 323-346.

Illing, R.B. and H. Wassle, 1979. Visualization of the HRP reaction product using the polarization microscope. Neurosc. Letters, 13: 7-11.

Isaacson, R.L., 1975. The myth of recovery from early brain damage. In: N.R. Ellis, Ed., Aberrant Development in Infancy, Potomac, M., Erlbaum, pp. 1-25.

Johnson, D. and C.R. Almli, 1978. Age, brain damage and performance. In: S. Finger, Ed., Recovery from Brain Damage: Research and Theory, New York, Plenum, pp. 115-134.

Jones, E.G. and R.Y. Leavitt, 1974. Retrograde axonal transport and the demonstration of non-specific projections to the cerebral cortex and striatum from thalamic intralaminar nuclei in the rat, cat and monkey. J. of Comp. Neur., 154: 349-378.

Jones, E.G. and S.P. Wise, 1977. Size, laminar, and columnar distribution of efferent cells in the sensory-motor cortex of monkeys. J. of Comp. Neur., 175: 391-438.

Kalil, K. and G. Schneider, 1975. Motor performance following unilteral pyramidal tract lesions in the hamster. Brain Res., 100: 170-174.

Kartje-Tillotson, G., E.J. Neafsey, and A.J. Castro, 1982. Electrophysiologic evidence for plasticity of the corticospinal projection after neonatal cortical lesions in rats. Anat. Rec. 202: 93A.

Kartje-Tillotson, G., E.J. Neafsey and A.J. Castro, 1983. Electrophysiological analysis of motor corticofugal plasticity after lesions in newborn rats. Submitted.

Kawaguchi, S. and T. Yamamoto. 1981. Reorganization of the cerebello-cerebral projection following hemicerebellectomy or cerebral cortical ablation. In: Lesion-Induced Neuronal Plasticity In Sensorimotor Systems. ed. H. Flohr and W. Precht, Springer-Verlag, New York.

Kaswaguchi, S., T. Yamamoto and A. Samejira, 1979a. Electrophysiological evidence for axonal sprouting of the cerebellothalamic neurons in kittens after neonatal hemicerebellectomy. Exp. Brain Res. 36: 21-39.

Kawaguchi, S., T. Yamamoto, A. Samejira, K. Itch and N. Mizuno, 1979b. Morphological evidence for axonal sprouting of cerebellothalamic neurons in kittens after neonatal hemicerebellectomy. Exp. Brain Res., 35: 511-518.

Kawamura, K. and T. Konno, 1979, Various types of corticotectal neurons of cats as demonstrated by means of retrograde axonal transport of horseradish peroxidase. Exp. Brain Res., 35: 161-175.

Kennard, M.A., 1936. Age and other factors in motor recovery from precentral lesions in monkeys. Amer. J. of Physio., 115: 138-146.

Kennard, M.A., 1940. Relation of age to motor impairment in man and in subhuman primates. Arch. of Neurol. and Psychiat., 44: 377-397.

Kennard, M.A., 1942. Cortical reorganization of motor function. Studies on series of monkeys of various ages from infancy to maturity. Archiv. of Neurol. and Phychiat. 48: 227-240.

Kievit, J. and H.G.J.M. Kuypers, 1977. Organization of the thalamo-cortical connexions to the frontal lobe in the rhesus monkey. Exp. Brain Res., 29: 299-322.

King, J.L., 1910. The cortico-spinal tract of the rat. Anat. Rec. 4: 245-252.

Kolb, B. and C. Holmes, 1983. Neonatal motor cortex lesions in the rat: absence of sparing of motor behaviors and impaired spatial learning concurrent with abnormal cerebral morphogenesis. Behav. Neurosci., 97: 697-709.

Kuypers, H.G.J.M., 1981. Anatomy of the descending pathways, In: J.M.

Brookhart and V.B. Mountcastle, Eds., Handbook of Physiology - The Nervous System II, Williams and Wilkens Co., Baltimore, pp. 597-666.

Kuypers, H.G.J.M., 1982. A new look at the organization of the motor system. Prog. in Brain Res., 57: 381-403.

Lawrence, D.G. and D.A. Hopkins, 1976. The development of motor control in the rhesus monkey: evidence concerning the role of corticomotoneuronal connections. Brain, 99: 235-254.

Leong, S.K., 1977a. Plasticity of cerebellar efferents after neonatal lesions in albino rats. Neurosci. Letters, 7: 281-289.

Leong, S.K., 1977b. Sprouting of the corticopontine fibers after neonatal cerebellar lesion in the albino rat. Brain Res., 123: 164-169.

Leong, S.K., 1980. A quantitative electron microscopic study of the corticopontine projections after neonatal cerebellar hemispherectomy. Brain Res., 194: 299-310.

Leong, S.K. and R.D. Lund, 1973. Anomoious bilateral corticofugal pathways in albino rats after neonatal lesions. Brain Res., 62: 218-221.

Lim, K.H. and S.K. Leong, 1975. Aberrant bilateral projection from the dentate and interposed nuclei in albino rats after neonatal lesions. Brain Res., 96: 306-309.

Liu, C-N. and W.W. Chambers, 1958. Intraspinal sprouting of dorsal root axons. Archives of Neurology and Psychiatry, 79: 46-61.

LiVolsi, G., C. Pacitti, V. Perciavalle, S. Sapienza and A. Urbano, 1982. Interpositus nucleus influences on pyramidal tract neurons in the cat. Neuroscience, 7: 1929-1936.

Lloyd, D.P., 1941. The spinal mechanism of the pyramidal system in cats. Neurophysiol., 4: 525-546.

Lund, R.D., 1978. Development and Plasticity of the Brain. Oxford Univ. Press, New York.

Lund, R.D. and K.E. Webster, 1967. Thalamic afferents from the dorsal column nuclei. J. of Comp. Neur., 130: 301-312.

Lundberg, A., 1975. Control of spinal mechanisms from the brain. The Nervous System. ed. D.B. Tower

Lundberg, A., U. Norrsell and P. Voorhoeve, 1962. Pyramidal effects on lumbo-sacral interneurones activated by somatic afferents. Acta. Physiol. Scand., 56: 220-229.

Lundberg, A. and P. Voorhoeve, 1962. Effects from the pyramidal tract on spinal reflex arcs. Acta. Physiol. Scand., 56: 201-219.

Martin, G., J.C. Bresnaham, C.K. Henkel and D. Megirian, 1975. Corticobulbar fibres in the north american opossum (Didelphis Marsupialis Virginiana) with notes on the Tasmanian brush-tailed possum (Trichosurus velpecula) and other marsupials. J. Anat., 120: 439-484.

Martin, G., A.O. Humbertson, Jr., L.C. Laxson, W.M. Panneton and I. Tschismadia, 1979. Spinal projections from the mesencephalic and pontine reticular formation in the north american opossum: A study using axonal transport techniques. J. Comp Neur., 187: 373-400.

Martin, G., T. Cabana, A.O. Humbertson, Jr., L. C. Laxson and W.M. Panneton, 1981. Spinal projections from the medullary reticular formation of the north american opossum: Evidence for connectional heterogeneity. J. of Comp. Neur., 196: 663-682.

Martin, G., T. Cabana, R. Waltzer, 1983. Anatomical demonstration of the location and collateralization of rubral neurons which project to the spinal cord, lateral brainstem and inferior olive in the north american opossum. Brain Behav. Evol., 23: 93-109.

Mihailoff, G.A., R.A. Burne and D.J. Woodward, 1978. Projections of the sensorimotor cortex to the basilar pontine nuclei in the rat: An autoradiographic study. Brain Res., 145: 347-354.

Mihailoff, G.A. and A.J. Castro, 1981. Autoradiographic and electron microscopic degeneration evidene for axonal sprouting in the rat corticopontine system. Neurosci. Lettes, 21: 267-273.

Mihailoff, G.A., C.B. Watt and R.A. Burne, 1981a. Evidence suggesting that both the corticopontine and cerebellopontine systems are each composed of two separate neuronal populations: An electron microscopic and horseradish peroxidase study in the rat. J. of Comp. Neur., 195:221-242.

Mihailoff, G.A., R.A. Burne, S.A. Azizi, G. Norell and D.J. Woodward, 1981b. The Pontocerebellar System in the Rat: An HRP study. II. Hemispheral Components. J. of Comp. Neur., 197: 559-577.

Miller, R.A. and N. L. Strominger, 1973. Efferent connection of the red nucleus in the brainstem and spinal cord of the rhesus monkey.

J. of Comp. Neur., 152: 327-346.

Milner, B., 1974. Sparing of language functions after early unilateral brain damage. In. E. Eidelberg and D.C. Stein, Eds., Functional Recovery After Lesions of the Nervous System, Neuroscience Research Program Bulletin, 12, pp. 213-216.

Murray, H.M. and M.E. Gurule, 1979. Origin of the rubrospinal tract of the rat. Nueorsci. Letters, 14: 19:23.

Nakamura, Y., Y. Kitao and S. Okoyama, 1983. Cortico-Darkscheritsch olivary projection in the cat: An electron microscope study with the air of horseradish peroxidase tracing technique. Brain Res., 274: 140-143.

Nakano, K., T. Takimoto, T. Kayahara, Y. Takeuchi, and Y. Kobayashi, 1980. Distribution of cerebellothalamic neurons projecting to the ventral neclei of the thalamus: An HRP study in the cat. J. of Comp. Neur., 194: 427:439.

Nation, W., M. Cox and D.R. Humphrey, 1983. Re-organization of the motor cortex of the rat following neonatal ablation of the opposite motor cortex. Anat. Rec., 205: 140-141A.

Neafsey, E.J., 1981. A simple method for glass insulating tungsten microelectrodes. Brain Res. Bull., 6: 95-96.

Neafsey, E.J. and C. Sievert, 1982. A second forelimb motor area exists in rat frontal cortex. Brain Res., 232: 151-156.

Nieoullin, A. and Y. Gahery, 1978. Influence of pyramidotomy on limb flexion movements induced by cortical stimulation and on associated postural adjustment in the cat. Brain Res., 149: 39-52.

Nyberg-Hansen, R. and A. Brodal, 1963. Sites of termination of corticospinal fibers in the cat. An experimental study with the Nauta method. Brain Res., 16: 39-54.

O'Donoghue, D.L., G. Kartje-Tillotson, E.J. Neafsey and A.J. Castro, 1982. Altered microstimulation thresholds in rat motor cortex following neonatal hemicerebellectomy. Neurosci. Abst. 8: 967.

O'Donoghue, D.L., G. Kartje-Tillotson and A.J. Castro, 1983. A comparison of rat motor cortical thresholds after hemicerebellectomy at different postnatal ages. Anat. Rec. 205: 146A.

Perciavalle, V., F. Santangelo, S. Sapienza, M.F. Serapide, and A.

Urbano, 1978. Motor responses evoked by microstimulation of restiform body in the cat. Exp. Brain Res., 33: 241-255.

Peterson, B.W., M. E. Anderson and M. Filion, 1974. Responses of ponto-medullary reticular neurons to cortical, tectal and cutaneous stimuli. Exp. Brain Res., 21: 19-44.

Peterson, B.W., R.A. Maunz, N.G. Pitts and R.G. Mackel, 1975. Patterns of projection and branching of reticulospinal neurons. Exp. Brain Res., 23: 333-351.

Price, A.W. and S.C. Fowler, 1981. Deficits in contralateral and ipsilateral forepaw motor control following unilateral motor cortical ablations in rats. Brain Res., 205: 81-90.

Ranck, J.B., Jr., 1975. Which elements are excited in electrical stimulation of mammalian central nervous system : A Review. Brain Res., 98: 417-440.

Sanderson, K.J., W.I. Welker and G.M. Shambes, 1982. Sensory and motor maps in rat sensorimotor cortex. Neurosci. Letters, 8: S77.

Sanderson, K.J., W.I. Welker and G.M. Shambes, 1984. Reevaluation of motor cortex and of sensorimotor overlap in cerebral cortex of albino rats. Brain Res., 292: 251-260.

Sapienza, S., B. Talbi, J. Jacquemin and D. Albe-Fessaro, 1981. Relationship between input and output of cells in motor and somatosensory cortices of the chronic awake rat. Exp. Brain Res., 43: 47-56.

Schneider, G.E., 1970. Mechanisms of functional recovery following lesions of visual cortex of superior colliculus in neonate and adult hamsters. Brain Behav. Evol., 3: 295-323.

Schneider, G.E., 1979. Is it really better to have your brain lesion early? A revision of the "Kennard Principle". Neuropsychologia, 17: 557-583.

Schneider, G.E., 1981. Early lesions and abnormal neuronal connections: Developmental rules can lead axons astray, with functional consequences. Trends in Neuroscience, 4: 187-192.

Schreyer, D.J. and E.G. Jones, 1982. Growth and target finding by axons of the corticospinal tract in prenatal and postnatal rats. Neurosc., 7: 1837-1853.

Schultz, W., E.B. Montgomery, Jr. and R. Marini, 1979. Proximal limb

movements in response to microstimulation of primate dentate and interpositus nuclei mediated by brain-stem structures. Brain, 102: 127-146.

Settlage, P.H., W.G. Bingham, H.M. Suckle, A.F. Borge and C.N. Woolsey, 1949. The pattern of localization in the motor cortex of the rat. Fed. Proc., 8: 144 (Abst.)

Shapovalov, A.I., 1972. Extrapyramidal monosynaptic and disynaptic control of mammalian alpha-motoneurons. Brain Res., 40: 105-115.

Smith, D.E. and A.J. Castro, 1979. Retrograde changes in Clarke's column following neonatal hemicerebellectomy in the rat. Am. J. of Anat., 156: 533-542.

Smith, R.L., S. Mosko and G. Lynch, 1974a. Role of various brain areas in recovery from partial cerebellar lesions in the adult rat. Behav. Bio., 12: 165-176.

Smith, R.L., S. Mosko and G. Lynch, 1974b. A comparison of the role of the morot cortex in recovery from cerebellar damage in young and adult rats. Behav. Bio., 12: 177-198.

St. James-Roberts, I., 1981. A reinterpretation of hemispherectomy data without functional plasticity of the brain. Brain and Language, 13: 31-53.

Stein, D.G., J.J. Rosen and N. Butters, 1974. Plasticity and Recovery of Function in the Central Nervous System, Academic Press, New York.

Stenvers, J-W., O. Eerbeek, J.M.B. Vianney De Jong, and A.E.F. Hugo Meijer, 1983. Motor activity and muscle properties in the hemidecerebellate cat. Brain, 106: 601-612.

Stewart, D.L. and A.H. Riesen, 1972. 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, pp. 171-211.

Strick, P.L., 1973. Light microscopic analysis of the cortical projection of the thalamic ventrolateral nucleus in the cat. Brain Res., 55: 1-24.

Strick, P.L., 1975. Multiple sources of thalamic input to the primate motor cortex. Brain Res., 88: 372-377.

Strick, P.L., 1976a. Activity of ventrolateral thalamic neurons during arm movement. J. of Neurophysiol., 39: 1032-1044.

Strick, P.L., 1976b. Anatomical analysis of ventrolateral thalamic input to primate motor cortex. J. of Neurophysiol., 39: 1020-1031.

Swenson, R.S. and A.J. Castro, 1982a. Plasticity of meso-diencephalic projections to the inferior olive following neonatal hemicerebellectomy in rats. Brain Res., 244: 169-172.

Swenson, R.S. and A.J. Castro, 1983. The afferent connections of the inferior olivary complex in rats. Anterograde study using autoradiographic and axonal degeneration techniques. Neurosci., 8: 259-275.

Swenson, R.S. and A.J. Castro, 1983. The afferent connection of the inferior olivary complex in rats: A study using the retrograde transport of horseradish peroxidase. Am. J. of Anat., 166: 329-341.

Teuber, H.L., 1975. Recovery of function after brain injury in man. In: Outcome of Severe Damage to the Central Nervous System (Ciba Foundation Symposium), Elsevier, Amsterdam, pp. 159-190.

Terreberry, R.R. and E.J. Neafsey, 1982. Cortical afferents to the vibrassae motor cortex in the rat. Cos. Neurosci. Abstr., 541.

Tomasch, J., 1969. The numerical capacity of the human cortico-ponto-cerebellar system. Brain Res., 13: 476-484.

Torvik, A., 1956. Afferent connections to the sensory trigeminal nuclei, the nucleus of the solitary tract and adjacent structures. J. of Comp. Neur., 106: 51-141.

Tracey, D.J., C. Asanuma, E.G. Jones and R. Porter, 1980. Thalamic relay to motor cotex: Afferent pathways from brainstem, cerebellum, and spinal cord in monkeys. J. of Neurophysiol., 44: 532-554.

Tsukahara, N., 1981. Synaptic plasticity in the mammalian central nervous system. Ann. Rev. Neurosci., 4: 351-379.

Tsukahara, N. and Y. Fujito, 1981. Neuronal plasticity in the newborn and adult feline red nucleus. In: Lesion-Induced Neuronal Plasticity In Sensorimotor Systems. ed. H. Flohr and W. Precht, Springer-Verlag, New York.

Ullan, J. and J. Artieda, 1981. Somatotopy of the corticospinal neurons in the rat. Neurosci. Letters, 21: 13-18.

Vahlsing, H.L. and E.A. Feringa, 1980. A ventral uncrossed

corticospinal tract in the rat. Exp. Neur., 70: 282-287.

Valverde, F., 1962. Reticular formation of the albino rat's brain stem cytoarchitecture and corticofugal connections. J. of Comp Neur., 119: 25-53.

Valverde, F., 1966. 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. Zeitschrift fur Zellforschung, 71: 297-363.

Welker, W., K.J. Sanderson and G.M. Shambes, 1984. Patterns of afferent projections to transitional zones in the somatic sensorimotor cerebral cortex of albino rats. Brain Res., 292: 261-267.

Wiesendanger, W., 1983. Cortico-cerebellar loops. Exp. Brain Res., Suppl. 7: 41-53.

Wise, S.P., J.W. Fleshman and E.G. Jones, 1979. Maturation of pyramidal cell form in relation to developing afferent and efferent connections of rat somatic sensory cortex. Neurosci., 4: 1275-1297.

Wise, S.P. and E.G. Jones, 1977. Cells of origin and terminal distribution of descending projections of the rat somatic sensory cortex. J. of Comp Neur., 175: 129-158.

Wise, S.P. and E.G. Jones, 1978. Developmental studies of thalamocortical and commissural connections in the rat somatic sensory cortex. J. of Comp. Neur., 178: 187-208.

Wise, S.P., E.A. Murray and J.D. Coulter, 1979. Somatotopic organization of corticospinal and corticotrigeminal neurons in the rat. Neurosci., 4: 65-78.

Woolsey, C.N., 1958. Organization of somatic sensory and motor areas of the cerebral cortex. In H. Harlow and C.N. Woolsey, Eds., Biological and Biochemical Bases of Behavior, University of Wisconsin Press, Madison, pp. 63-81.

Woolsey, C., T. Gorska, A. Wetzel, T. Erickson, F. Earls and J. Allman, 1972. Complete unilatral section of the pyramidal tract at the medullary level in macaca mulatta. Brain Res., 40- 119-123.

Yamamoto, T., S. Kawaguchi and A. Samejima, 1979. Electrophysiological studies on the cerebellocerebral projection in the rat. Exp. Neurol., 63: 545-558.

Yamamoto, T., S. Kawaguchi and A. Samejima, 1981. Electrophysiological studies on plasticity of cerebellothalamic neurons in rats following neonatal hemicerebellectomy. Jpn. J. Physiol., 31: 217-224.

Yu, J., W.W. Chambers, and C. Liu, 1979. Instrumental conditioned responses in cats with bulbar pyramid and red nucleus lesions. Neurobiol. Exp., 39: 219:226.

Zimmerman, E.A., W.W. Chambers, and C.N. Liu, 1964. An experimental study of the anatomical organization of the cortico-bulbar system in the albino rat. J. of Comp. Neur., 123- 301-324.

APPROVAL SHEET

The dissertation submitted by Daniel L. O'Donoghue has been read and approved by the following committee:

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

Dr. Mary D. Manteuffel
Associate Professor, Biochemistry, Loyola

Dr. John A. McNulty
Associate Professor, Anatomy, Loyola

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

Dr. Robert D. Wurster
Professor, Physiology, Loyola

Dr. James C. Hazlett, ex-official
Associate Professor, Anatomy, Wayne State University

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 full 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.

April 12, 1984
Date

Anthony J. Castro
Anthony J. Castro, Ph.D.
Director