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Role of Various Brain Areas in Recovery from Partial Cerebellar Lesions in the Adult Rat

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Several experiments were performed to assess: (1) the effects of partial cerebellar lesions on gross locomotion, balance, and posture in the rat; (2) the rate and degree to which deficits are compensated; and (3) the location of brain systems responsible for recovery. On our tests, lesions of the lateral cerebellar cortex produce no motor or postural deficits. As in other species, unilateral lesions of the vermal cortex produce ipsilateral limb extension, while hemicerebellectomies and lesions of the entire fastigial nucleus, or only its rostral part, produce contralateral limb extension. Lesions of the caudal fastigial nucleus alone produce symptoms similar to a vermal cortex lesion. Animals with medial cortex lesions had recovered by 10-15 days postoperatively, while those with fastigial nucleus lesions or hemicerebellectomies showed complete recovery by 30-35 days. Those animals which suffered gliosis or chromatolysis within the lateral vestibular nucleus showed more persistent symptoms. Finally, secondary-lesion experiments suggest that circuits through the contralateral fastigial nucleus, rather than the motor cortex, are primarily responsible for recovery after unilateral cerebellectomy in the adult rat.

INTRODUCTION

It is fairly common for the behavioral deficits resulting from central nervous system damage to attenuate with sufficient postoperative time. Despite frequent notice of this phenomenon, little is understood regarding the mechanisms underlying such functional recovery. Recovery must depend on adjustments in remaining, intact tissue. Thus, in order to specify the nature of these adjustments, it is logical to study regions and systems anatomically or functionally related to the damaged area. In many ways the cerebellum is

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well-suited for this purpose; its anatomical (Jansen and Brodal, 1954; Chambers and Sprague, 1955; Goodman and Simpson, 1961; Brodal, 1967; Evarts and Thach, 1969) and physiological (Eccles, Ito, and Szentágothai, 1969) relationships are well studied, and the behavioral deficits resulting from damage to it are readily characterized (e.g., Dow and Moruzzi, 1958). In addition, several authors have examined the time course and general nature of functional recovery after cerebellar damage (Carrea and Mettler, 1947; Batini and Pompeiano, 1957; Sprague and Chambers, 1959; Manni and Dow, 1963).

The present experiments were designed to explore the anatomical systems responsible for postural and locomotor recovery after cerebellar lesions in the rat. This information should provide a basis for later physiological and chemical studies of the relevant processes at cellular and synaptic levels. Since relatively little work has been done with cerebellar lesions in rats (Manni and Dow, 1963; Lipton, 1966; Peters and Filter, 1973) it was first necessary to assess the nature of motor deficits caused by partial or complete cerebellar damage. The intent of these first experiments, then, was not to measure precisely the syndromes produced by the lesions, but rather to establish whether or not they conform at an observational level to the well-defined pattern reported for cats and primates.

EXPERIMENT 1

Methods

Male albino Sprague-Dawley rats weighing between 275 and 350 g were used in both experiments. The animals were housed in group cages until the time of surgery, after which they were maintained in individual colony cages with sawdust floors. Animals received one of four surgical treatments:

A. Unilateral aspirated lesions of the lateral cerebellar cortex ($N = 3$)
B. Unilateral aspirated lesions of the medial (vermal) cerebellar cortex ($N = 6$)
C. Aspirated hemicerebellectomies ($N = 20$)
D. Unilateral electrolytic lesions of the fastigial nucleus ($N = 28$)

All lesions were performed under nembutal anesthesia, 50 mg per kg. The aspirated lesions were done using a fine glass pipet with the aid of a dissecting microscope. The electrolytic lesions were placed with a stainless-steel electrode, insulated except for 0.5 mm at the tip, using 1.5 mA anodal current for times varying from 30 to 60 sec. All animals received a single, postsurgical injection of Duricillin.

After surgery, all animals were tested every 5-7 days for subjective evaluation of performance on a battery of postural and locomotor measures. These included coordination in walking, head or body tilt, ability to stand or sit without falling, and presence of abnormal muscle tonus in the limbs or

neck. In addition, most animals were given three trials during each test period to measure their ability in running down a straight, darkened Plexiglas alley. This alley measured 12 X 90 cm, and was equipped with touch circuits 10 cm apart along the entire length. Normal animals run quickly through with very few contacts on either side. In operated rats, this alley was used as a quantitative measure of any resulting postural asymmetry. Scores from the alley trials over each test period were averaged for each animal. These individual means were then pooled within like-lesion groups to obtain group means. These values were used for statistical comparisons with a *t*-test.

After completion of all testing, the animals were perfused through the heart with 10% formol saline. The brains were fixed for varying periods in the same solution, then sliced on a freezing microtome at 50 μm. Sections through the lesions were stained with cresyl violet, and lesions reconstructed for comparison.

Results

Reconstruction of maximum and minimum lesions from the four surgical groups are presented in Fig. 1.

Lateral cortex lesions were centered between lobules 5 and 8 (according to Larsell, 1952). In all cases, these lesions were lateral to the paramedian fissure and did not include the paraflocculus.

Vermal cortex lesions were of the same relative size as the lateral group; however, these included cortex medial to the paramedian fissure, between lobules 4 and 8.

Aspirated hemicerebellectomies ranged from a minimum, in which only the fastigial nucleus, part of the interpositus nucleus, and the vermal cortex were damaged, to a maximum, in which removal of one-half the cerebellum up to the midline was complete. Additional damage to the superior and inferior cerebellar peduncles was variable, but in none of these animals was there direct damage to the dorsal brainstem. However, in six animals, microscopic analysis revealed some gliosis or chromatolysis in parts of the lateral vestibular nucleus.

Electrolytic lesions of the fastigial nucleus were complete in 18 rats, destroyed only the caudal extent in three animals, and only the rostral part in three others. Among these, the damage to the neighboring interpositus nucleus was variable but slight; additional damage was present in some cases to the inferior cerebellar peduncle, and to the medullary core of the cerebellum. Five electrolytically lesioned animals suffered additional damage to the dorsal area of the lateral vestibular nucleus on one side. Four other animals showed some gliosis or chromatolysis in that brainstem area upon microscopic analysis. Four remaining animals in the electrolytic group suffered no apparent damage to

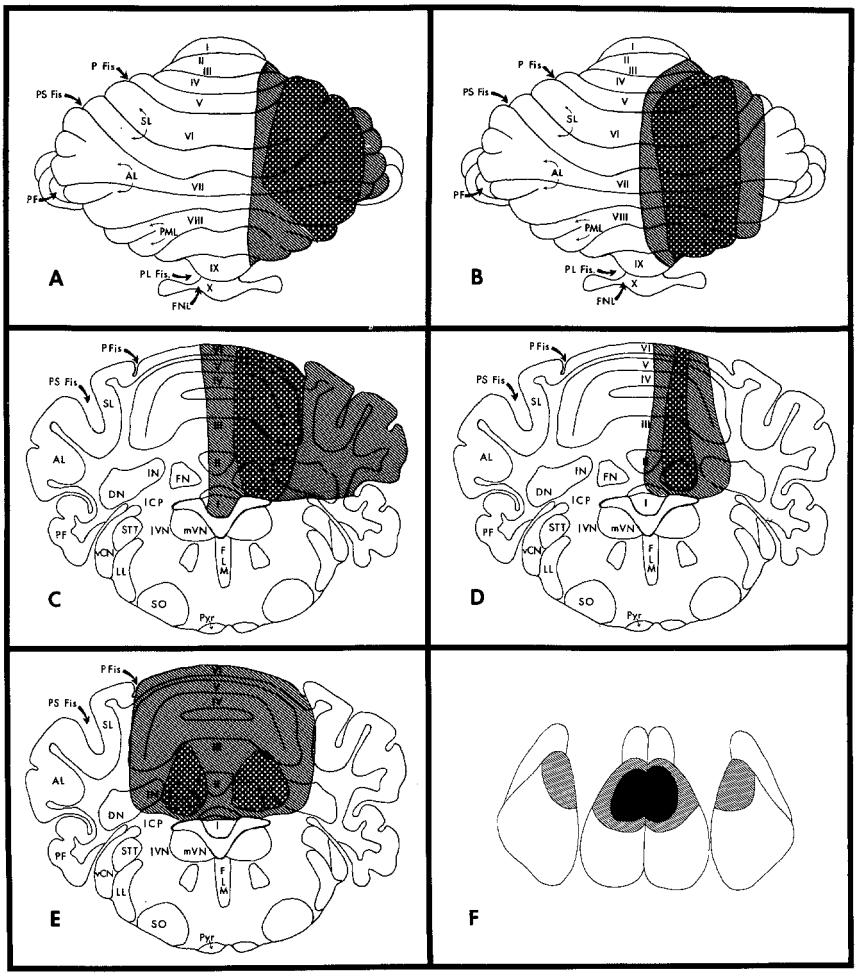

Fig. 1. Reconstructions representing minimum (checked) and maximum (striped) lesion damage in each of the operative groups: (A) lateral cerebellar cortex; (B) medial cerebellar cortex; (C) aspirated hemicerebellar lesions; (D) unilateral electrolytic lesions of the fastigial nucleus; (E) two-stage bilateral electrolytic lesions of the fastigial nucleus; (F) aspirated lesions of the rostral neocortex. AL, ansiform lobe of cerebellum; AN, nucleus ambiguous; DN, dentate nucleus; FLM, medial longitudinal bundle; FN, fastigial nucleus; FNL, flocculonodular lobe of cerebellum; ICP, inferior cerebellar peduncle; IN, interpositus nucleus; LL, lateral lemniscus; lVN, lateral vestibular nucleus; mVN, medial vestibular nucleus; PF, paraflocculus; P FIS, prime fissure; PML, paramedian lobe of cerebellum; PS FIS, posterior superior fissure; Pyr, pyramid; SL, simple lobe of cerebellum; SO, superior olive; STT, spinal tract of the trigeminal nerve; vCN, ventral cochlear nucleus; vSCT, ventral spinal-cerebellar tract; V, trigeminal nerve; VII, facial nerve; I-X, cerebellar lobules according to Larsell (1952).

the fastigial nucleus or to other deep nuclear groups within the cerebellum; that is, these lesions were located anterior to the nuclei, totally within the anterior cerebellar cortex.

The lateral cortical lesions produced no apparent loss in initiation of locomotor activity, in coordinated walking, balance in sitting or standing, or in general posture. These results were reflected in the alley scores, which gave no indication of greater tendency to touch either side. ($P > 0.05$) (Table 1, column A).

Lesions restricted to the medial cortex caused a hyperextension of the ipsilateral fore- and hindlimbs, with the predominant effect being in the hindlimbs. There was also a weakness, but rarely an active hyperflexion, in the contralateral limbs. The animals showed a strong tendency to lean away from the side of the lesion, often with a corresponding contralateral circling during locomotion. In the alley they repeatedly touched the side contralateral to the lesion; this tendency was significantly decreased ($P < 0.02$) by 10-15 days postlesion (Table 1, column B). Complete recovery of coordinated walking, balance, and ability to initiate movements smoothly was accomplished in all animals at least by the 40th postoperative day.

Aspirated hemicerebellar lesions of all sizes, or electrolytic lesions destroying the rostral or entire fastigial nucleus, resulted in a syndrome that was nearly the opposite to that produced by lesions restricted to the vermal cortex. That is, these animals had a marked weakness in the limbs ipsilateral to the lesions and a hyperextension of the contralateral limbs, particularly of the hind limbs. When placed on an open surface, these animals initiated movement less frequently than normal; when they did walk, they tended to fall to the side of the lesion and to circle in that direction. Movements tended to occur in sudden, rapid bursts rather than smooth, exploratory-type walking typical of normal rats. In the alley, these animals primarily touched the side toward the lesion. By subjective tests, these animals all recovered normal balance, locomotion, and posture by the 40th postoperative day. Similar data were obtained in the alley (Table 1, columns C and E) where side contacts gradually returned to normal levels by 30-35 days for both complete aspirated and electrolytic groups ($P > 0.05$). Recovery from rostral fastigial nucleus lesions appeared subjectively to follow a similar time course; however, alley tests were unfortunately not performed.

In three of the rats with electrolytic fastigial lesions, only the caudal extent of that nucleus was destroyed. This portion of the nucleus gives rise almost entirely to crossed fastigial-vestibular fibers through the hook bundle (Matsushita and Iwahori, 1971). In agreement with earlier studies (e.g., Batini and Pompeiano, 1957), the symptoms appeared in these animals as a mirror image of those which followed total fastigial nucleus lesions. The deficits were slightly milder, and appeared to recover in less time than required for animals

TABLE 1

Mean Alley Scores for Primary Lesion Groups Over Time[a]

Days post-operative	A Lateral cerebellar cortex lesion (N=3)	B Medial cerebellar cortex lesion (N=6)	C Hemi-cerebellectomy (N=12)	D Hemi-cerebellectomy with partial LVN chromatolysis (N=6)	E Unilateral fastigial nucleus lesion (*N*=8)	F Unilateral fastigial nucleus lesion with partial LVN chromatolysis (N=4)	G Bilateral motor cortex lesion (*N*=4)
0	1.02 ± 0.24	1.42 ± 0.34	0.79 ± 0.26	0.79 ± 0.26	0.98 ± 0.22	0.98 ± 0.22	0.54 ± 0.11
1-5	1.36 ± 0.58	7.87 ± 1.37	11.82 ± 1.95	16.21 ± 4.70	10.20 ± 1.45	9.22 ± 2.07	0.62 ± 0.28
10-15	0.97 ± 0.46	0.98 ± 0.34	4.61 ± 0.67	9.80 ± 1.28	3.63 ± 1.04	7.21 ± 0.58	1.50 ± 0.74
30-35	0.82 ± 0.23	0.89 ± 0.29	2.09 ± 0.47	7.72 ± 0.77	2.15 ± 0.29	7.46 ± 0.40	1.74 ± 0.24

[a]Note: Scores represent means ± the standard error of the mean.

with total fastigial nucleus damage; however, again alley scores are not available for these animals.

In all of the four electrolytic and the six aspirated subjects which appeared to sustain some gliosis or chromatolysis in parts of the lateral vestibular nucleus, subjective analysis showed that recovery was more slow and less complete. Contacts with the sides of the alley did not decrease significantly even by 50-55 days in either group ($P > 0.05$). Aspirated subjects were sacrificed at that time; however, electrolytic animals were maintained at least until postoperative day 100, at which time their alley scores were significantly decreased from the 50- to 55-day test ($P < 0.02$) and not different from preoperative levels ($P > 0.05$). Whether the more damaged aspirated subjects would have recovered by that late time cannot be determined.

Lesions in five animals which encroached upon and destroyed cells in the dorsal aspect of the lateral vestibular nucleus caused a very dramatic and invariant effect: the rats would roll almost incessantly to the side of the damage. Locomotion was impossible (hence no alley tests were made) and the rats would continue the rolling behavior for some minutes after being disturbed. In addition, the eyes were protruded and acutely turned away from the side of the lesion. These symptoms appeared to be permanent. Even after 160 days of recovery, these rats had not regained the ability to walk, and still persisted in the rolling behavior seen immediately after surgery. The effects of the lesions on eye position also remained evident throughout the testing period.

EXPERIMENT 2

The purpose of this experiment was to localize the brain regions participating in the recovery seen after unilateral lesions of the fastigial nucleus and hemicerebellectomies. It has been reported that discrete lesions of motor cortex will reinstate some symptoms of unilateral cerebellar damage in primates (Carrea and Mettler, 1947; Carpenter and Stevens, 1957; Goldberger and Growden, 1969) and cats (Batini and Pompeiano, 1957; Sprague and Chambers, 1959). The possible roles of other, motor-related brain areas apparently have not been studied to date.

Methods

In eight rats which had recovered from hemicerebellar lesions, secondary lesions were placed bilaterally in the rostral 1/3 to 1/2 of the neocortex by aspiration. These operations were performed 40 days after the first cerebellar surgery, using similar operative procedures.

In 10 rats recovered from unilateral electrolytic lesions of the fastigial nucleus, secondary lesions were placed electrolytically in the remaining, contralateral fastigial nucleus.

Four naive animals were lesioned bilaterally by aspiration in the rostral neocortex. Forty days later, these animals were given aspirated hemicerebellar lesions.

Testing and statistical procedures were the same as in Experiment 1.

Results

Reconstruction of maximal and minimal damage through the neocortex and contralateral fastigial nucleus are presented in Fig. 1.

The secondary neocortical lesions produced no obvious impairments of locomotion, balance, or posture in any of the recovered rats; that is, the lesion failed to reinstate the initial cerebellar syndrome. An insignificant change ($P > 0.05$) in postoperative alley scores on these animals supports this finding (Table 2).

In the four naive animals which received primary neocortical lesions, posture and locomotion were not appreciably impaired on the subjective tests. In addition, alley contacts did not increase significantly ($P > 0.05$) any time after surgery (Table 1, column G). After secondary surgery for the hemicerebellectomy, alley contacts increased ($P < 0.01$), but returned to near normal levels ($P > .05$) by 30-40 days (Table 2). Subjective evaluations of posture showed a similar course for recovery.

Electrolytic lesions of the contralateral fastigial nucleus in "unilaterally-recovered" rats produced a marked bilateral reduction of extensor tonus in

TABLE 2

Mean Alley Scores for Secondary Lesion Group Over Time[a]

Days post-operative	A	B	C
	Motor cortex lesion after hemicerebellectomy (N=4)	Hemicerebellectomy after motor cortex lesion (N=4)	Contralateral fastigial nucleus lesion (N=6)
0	2.42 ± 0.73	1.30 ± 0.49	2.14 ± 0.85
1-10	3.63 ± 1.47	8.94 ± 1.08	11.92 ± 1.90
11-20	0.83 ± 0.44	6.81 ± 2.68	11.65 ± 1.66
21-30	0.89 ± 0.49	4.02 ± 0.82	8.53 ± 2.45
31-40	–	2.17 ± 0.66	7.70 ± 2.86

[a]Note: Scores represent the means ± the standard error of the mean.

the hind limbs. The effects of the second lesion on forelimb tonus was variable between animals. In some rats, the limb ipsilateral to the second lesion was weak while the contralateral limb was extended; in others both forelimbs showed a hypotonus. Alley scores were markedly increased ($P < 0.01$) and in all cases, recovery from the secondary lesion was slow and incomplete ($P > 0.05$) even by 80 postoperative days (Table 2).

DISCUSSION

While no attempt was made to establish the precise pattern of deficits produced by each lesion, sufficient information was collected to indicate that lesions of the medial cerebellar cortex, fastigial nucleus, and the lateral vestibular nuclei produce effects that are very similar to those seen after damage to these structures in carnivores and primates. On the basis of lesion studies done in these species, Sprague and Chambers (1959) and Batini and Pompeiano (1957) concluded that the vermal cortex suppresses the fastigial nuclei which in turn facilitate the vestibular nuclei. The lateral vestibular nucleus exerts an extremely potent facilitory action on ipsilateral alpha motor neurons responsible for extension (Eccles *et al.*, 1967). From our data it appears that similar patterns of postural function are present in medial aspects of rat cerebellum.

The relative lack of effects seen after lesions of the lateral cerebellar cortex is consistent with the findings of Peters and Filter (1973). This may be due to two facts: first, it is commonly hypothesized that the hemispheric regions of the cerebellum are involved with the control of fine or detailed movements (which were not assessed in the present studies); second, these areas of rat cerebellum are obviously less developed than in carnivores and primates, animals which do reveal motor deficit from such lesions.

The data for recovery after fastigial lesions agree with those reported for total unilateral lesions in this species (Manni and Dow, 1963). It is interesting to note that in this study, type or size of lesions did not seem to influence the extent of the deficit on the rate or degree of recovery; thus, electrolytic lesions of the fastigial nucleus produced symptoms as severe as much larger aspirated vermal cortex plus fastigial lesions or total hemicerebellectomies, and all recovered at about the same speed.

The experiments with secondary lesions provide some interesting clues regarding the brain systems involved in the recovery seen after lesions of the fastigial nuclei. The failure of the anterior cerebral cortex lesions to disturb postural and locomotor recovery is at variance with the findings of comparable studies involving primates and cats. However, this discrepancy may reflect the great evolutionary differences seen in the connections of this brain area between species. In fact, Dow and Moruzzi (1958) noted that the motor

cortex seemed more critical to the recovery from cerebellar symptoms in primates than in cats.

More difficult to explain is the apparent difference in the present findings with those of Manni and Dow (1963). These authors applied cobalt powder to one side of the anterior neocortex of rats during the postoperative period after total cerebellectomy. They found that this procedure produced a worsening or recurrence of the cerebellar symptoms. However, the histology which they presented is inadequate to determine the extent of the cobalt damage. In addition, the authors did not discuss the symptoms which may result from the cobalt lesion in a naive animal, or the effects of this treatment on an "unrelated" brain area in recovered cerebellar-damaged animals. In relation to this, Van Hasselt (1973) has shown that transient (1-2 days) motor disturbances appear in rats with unilateral ablations of the motor cortex. These symptoms appear similar to and could be mistaken for some of the effects of unilateral cerebellar damage: ipsilateral limb extension and contralateral limb retraction, with corresponding contralateral circling. In Manni and Dow's study it is possible that one effect of the cobalt was to cause these lesion effects to be maintained.

The brain area which appeared more directly involved in unilateral cerebellar recovery in the present study is the contralateral cerebellum. In the study using secondary, contralateral fastigial nucleus lesions one of two effects might reasonably have been predicted:

(1) If recovery from the initial lesion were occurring outside the contralateral cerebellum, then the secondary fastigial lesion would be expected to yield a unilateral cerebellar syndrome (i.e., ipsilateral weakness of limbs, etc.).

(2) If, on the other hand, the contralateral fastigial nucleus were involved in recovery from the initial fastigial lesion, then the secondary lesion should produce persistent bilateral deficits (i.e., bilateral weakness of limbs, oscillatory locomotion, etc.). Since the second result, bilateral deficit, was obtained (at least in the hind limbs), it appears that recovery from the initial lesion involved a circuit through the remaining fastigial nucleus. This conclusion is supported by the finding that in the one animal which survived a single-stage bilateral fastigial nucleus lesion (not included in the study) there was little or no motor or postural recovery on our measures. Clearly, we will need additional information regarding the effects of one-stage bilateral fastigial nucleus damage in order to compare this directly with the recovery reported for two-stage ablation, and also to comment further on the involvement of the contralateral nucleus in the postural and locomotor compensation after unilateral fastigial nucleus damage. However, Manni and Dow (1963) have reported that bilaterally lesioned rats will reach a stage of "stabilized deficiency," but do not completely recover motor abilities. Presumably, this result would not be obtained in species where other structures, such as motor

cortex, are capable of adjusting for the loss of the fastigial nuclei; in fact, cats and monkeys show remarkable recovery from bilateral cerebellar lesions.

In addition, it should be noted that the lateral vestibular nuclei must play an important role in the final functional recovery after unilateral cerebellar or fastigial ablation. Thus, in those animals which suffered direct brainstem damage, cerebellar symptoms were augmented by the severe opisthotonus and rolling behavior characteristic of vestibular damage. These symptoms themselves never showed any amelioration, and continued to mask any possible recovery of the comparatively milder cerebellar deficits. Also, those animals which showed gliosis or chromatolysis in the lateral vestibular nuclei were more persistently, though not necessarily more severely, debilitated as measured both subjectively and in the alley tests. It is probable that symptoms more directly related to vestibular damage confound the recovery which normally proceeds after simple cerebellar damage. It may also be that the cerebellar recovery represents some adjustments in the remaining contralateral circuitry, which must, therefore, also involve the vestibular complex on one or both sides. A further analysis of the mechanisms underlying this instance of behavioral recovery must await physiological analysis of the remaining, related areas within the cerebellum and brainstem.

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