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Neuroanatomical status of monkeys showing functional compensation following neonatal cerebellar lesions*

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Summary. Neuroanatomical changes observed at the light microscopic level in various brain areas of four adult monkeys, who had various degrees of cerebellar ablation shortly after birth, are described in this study. Extensive neonatal hemilateral ablations of the cerebellar cortex (sparing the nuclei), which have previously been shown to leave the adult monkey with no discernible motor deficits, lead to substantial degeneration, mainly within the remaining cerebellum and the brain stem. In particular: 1) Ipsilateral to the lesion the intracerebellar nuclei and to some extent also the lateral vestibular nucleus are clearly reduced in size, whereas the contralateral cerebellum appears normal. 2) The principal olive and parts of the pontine nuclei show massive degeneration contralateral to the lesion. 3) Among the nuclei efferent to the cerebellum only the red nucleus contralateral to the lesion shows clear signs of degeneration. 4) Morphometric analysis of motor cortex and pyramidal tract reveals no systematic differences between the left and right sides, nor any other morphological indication of compensation. The morphological abnormality pattern in our monkeys is particularly similar to that described in cases of humans with olivo-pontocerebellar atrophies.

Key words: Cerebellectomy – Neonatal lesions – Neuroanatomical status – Monkey

Introduction

It is well known that cerebellar lesions, particularly if incurred early in life, inevitably lead to marked neuroanatomical changes in functionally adjacent brain areas (Brodal 1940; Castro 1978; Harkmark 1956). These, however, are usually not considered in experimental studies concentrating on the extent of the cerebellar lesion and its functional effects on various motor systems. On the other hand most clinical case reports of asymptomatic (i.e. well compensated) cerebellar malformations traditionally emphasize the histological abnormalities at various locations in the brain stem and even the neo-cortex with signs of degeneration as well as enlargement (Anton 1903; Hitzig 1884; Neubürger and Edinger 1898; Rubinstein and Freeman 1940; Stewart 1956). Since any functional changes might be caused not only by the primary loss of cerebellar tissue but also in part by secondary degenerative or compensatory effects, it seems necessary to include the extracerebellar parts of the brain in an adequate description of neuroanatomical correlates of these functional deficits and their possible compensation.

In this paper we report on neuroanatomical changes in various brain areas of four macaque monkeys who underwent total or partial cerebellectomy as infants. Functional aspects of these lesions and their compensation as illustrated in detail by oculomotor performance examination in a large group of monkeys have been published recently (Eckmiller and Westheimer 1983). The neuroanatomical status seen at the light microscopic level of these selected monkeys is particularly astonishing in the light of our finding that functional compensation of extensive neonatal cerebellar lesions with subsequent severe degeneration in various brain stem nuclei was virtually complete if the cerebellar nuclei had been spared from the initial surgery.

Moreover, the present neuroanatomical study, in conjunction with the previous functional description of long term effects of neonatal cerebellectomy, allows a comparison of distinct histological abnor-

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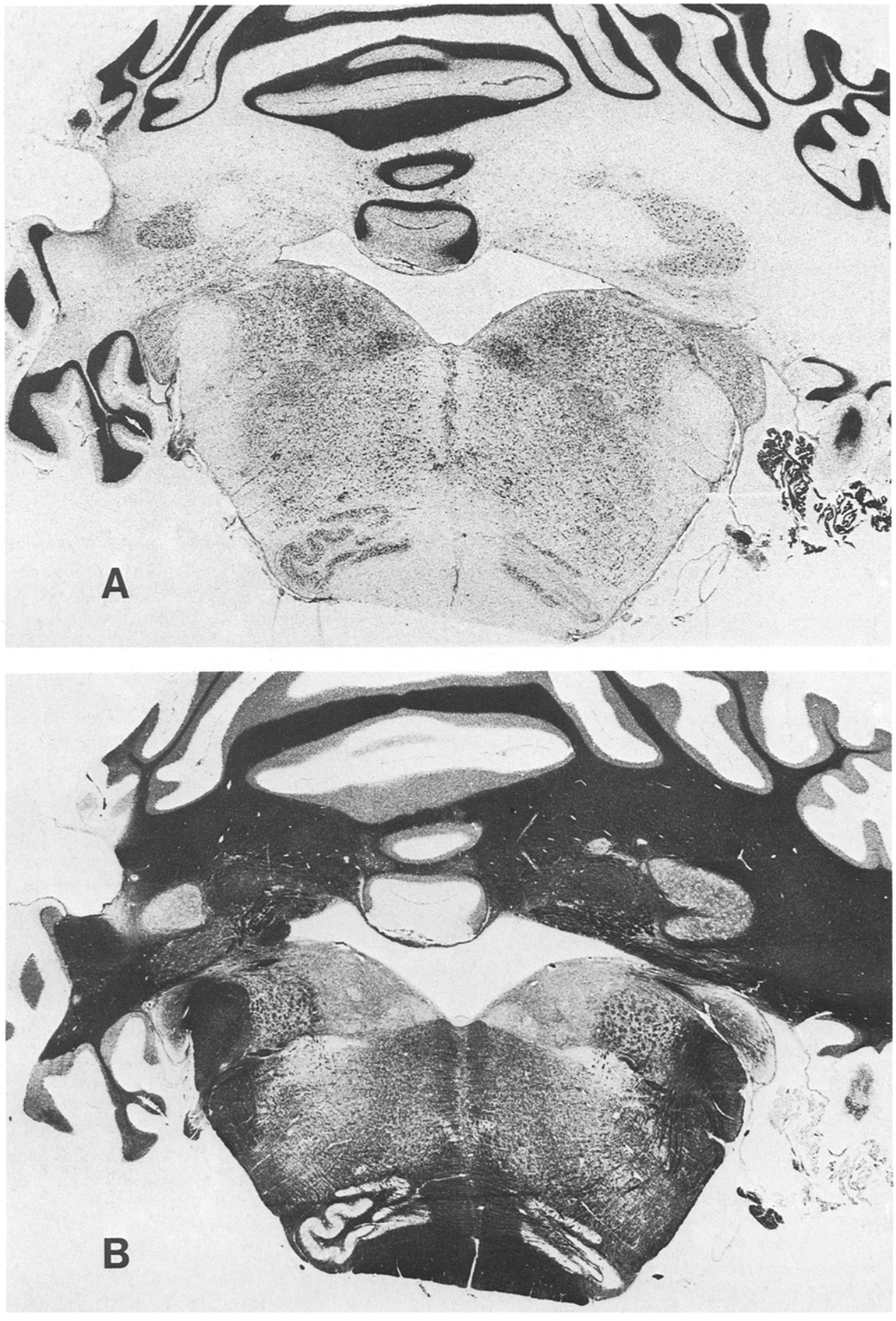

Fig. 1A and B.

mality patterns throughout the brain with those of human cases of cerebellar malformation.

Methods

Preparation of the brains

Four monkeys were perfused under deep Nembutal anesthesia with 200 ml Saline followed by 1,500 ml of 10% Formaline-Saline (both solutions were kept at body temperature) into the left ventricle. After careful removal of the brain, the basal half of the cleaned skull was mounted in a stereotaxic headholder. The brain was then placed in the skull and cut in the frontal plane into several slabs at the stereotaxic coordinates of A 20, A 10, AP 0, and P 10 by means of a scalpel blade attached to a micromanipulator. The most posterior cut at P 10 was restricted to the cerebellar hemispheres such that the posterior parts of the cerebellum remained attached to the most posterior slab (reaching from AP 0 to P 10). These slabs were kept in the fixative (10% Formaline-Saline) for up to eight months.

Embedding and staining

An accelerated celloidin embedding method (Eckmiller and Jaworski, unpublished) was applied which speeds up the embedding process from 6–8 weeks to only 2–3 weeks by using a combination of higher temperatures (30–40° C) and partial vacuum (350–550 Torr). Serial whole sections from the individual brain slabs in the frontal plane were subsequently obtained (25 μm thick) using a large sliding microtome (Tetrander, Jung) with a microtome knife with b-polish; each section being numbered with a felt pen just before the cut. This method has the advantage of yielding rather sturdy sections that can be stored for several months in 70% Ethanol.

Every 5th section was stained with Nissl cell stain (cresyl-violet) and the following section with fiber stain (modified Weigert). The remaining sections were stored for future use.

Microscopic-examination and morphometry

Both direct microscopic examination and microprojected image analysis were utilized.

Planimetry of both the pyramidal tracts (× 16) and parts of the cerebral cortex (× 6) was performed by means of a mechanical planimeter (Haff 317) and occasionally controlled with a computerized planimetry system (Videoplan, Kontron). For comparison, brains of non-operated monkeys which had been processed by the same histologic methods were available.

Results

A more general description of the extent of the lesions and the status of the remaining parts of the cerebellum has been previously given (Eckmiller and Westheimer 1983), together with a detailed analysis of the oculomotor status of these animals.

The present study is based on the normal or abnormal appearance, i.e., reductions in nuclear size, atrophy or actual cell loss, reduction in the intercellular neuropil, changes in cell density, or other gross changes in the nuclei or areas as evident at the light microscopical level (Fig. 1). The following qualitative and subjective scale was drawn up to assess the extent of the atrophic and degenerative changes present on one or both sides of the brain: Normal, almost normal, slightly reduced, clearly reduced, strongly reduced, almost completely degenerated, completely degenerated (Table 1, 2). These designations were obtained by constructing special anatomical status tables for each structure describing the normality or extent of abnormality in each section through the whole series where the structure was present on either one or both sides. The term "normal" was used only if there were no signs of lesion, atrophy or cellular degeneration even in comparison with normal monkey brains. Atlases of monkey brains (Madigan and Carpenter 1971; Shantha et al. 1968; Snider and Lee 1961) were also used for comparison. In general, it must be emphasized that in response to partial cerebellar ablation, the remaining cerebellum, together with the adjacent brain stem, was found to be clearly distorted in comparison to the bilateral symmetry found in normal monkeys. This distortion (up to several millimeters on the left relative to the right side) is worth mentioning, because examination of single sections in the frontal plane might lead to the wrong impression of asymmetries in size and occurrence of a structure; judgments in these matters must, therefore, be based only on complete sets of serial sections.

I. Extent of lesions, appearance of remaining cerebellum, case histories (Fig. 2; Table 1)

Monkey B. Macaca arctoides, male, age 4 years, body weight: 7.1 kg. Cerebellar ablation within the first week after birth was almost complete and included the intracerebellar nuclei. At variance with our previous report (Eckmiller and Westheimer 1983) also the left lobulus paramedianus was completely absent, and the left paraflocculus and flocculus had been clearly reduced by partial ablation and subsequent atrophy. A small portion of the left nucleus dentatus was also detected adjacent to the remaining portion of the left flocculus. Even the

Fig. 1A and B. Photomicrographs of a typical pair of cell (upper) and fiber stained (lower) sections which were used for microscopic evaluation of anatomical status. (Monkey D, frontal sections at the level of inferior olives)

Table 1. Neuroanatomical status of the remaining cerebellum in monkeys with neonatal cerebellar ablations

	Monkey B		Monkey D		Monkey F		Monkey I	
	L	R	L	R	L	R	L	R
A. Cerebellar Cortex								
Lobus anterior	absent	absent	normal	normal	normal	normal	normal	extensive lesion or atrophy
Lobulus simplex	absent	absent	normal	normal	normal	almost normal	normal	absent
Lobulus ansiformis	absent	absent	normal	absent except for part of Crus I	almost normal	absent	atrophy in part of Crus I	absent
Lobulus paramedianus	absent	absent	normal	absent	normal	extensive lesion or atrophy	normal	absent
Paraflocculus	extensive lesion; some atrophy	absent	normal	some lesion anterior part	normal	extensive lesion or atrophy	normal	absent
Flocculus	partial lesion some; atrophy	absent	normal	reduced to half by lesion, atrophy	normal	extensive lesion some; atrophy	normal	absent
Vermis	absent except for small atrophic rudiment in anterior part		normal except for lesion and atrophy on right side of VII, VIII, and IX		normal except for some atrophy on right side of VIII and IX		extensive lesion or atrophy except for normal nodulus	
B. Intracerebellar nuclei								
N. fastigii (F)	absent	absent	normal	slightly reduced	normal	almost normal	normal	clearly reduced
N. interpositus (I)	absent	absent	normal	clearly reduced	normal	clearly reduced	normal	clearly reduced
N. dentatus (D)	reduced by lesion and atrophy	absent	normal	clearly reduced by lesion and atrophy	normal	clearly reduced by lesion and atrophy	normal	clearly reduced
C. Vestibular Nuclei								
N. vestibularis lateralis (VL)	slightly reduced	clearly reduction	normal	normal	normal	slightly reduced	normal	slightly reduced

remaining cerebellar rudiments contained considerably large atrophic areas (as indicated in Fig. 2 by broken lines in the cerebellar cortex, hatched cortical region at level P4 (arrow), reduced dentate nucleus (D) at P7). The brachium conjunctivum (BC) (at P1) was very small on the left side and totally absent on the right. A small atrophic rudiment of the cerebellar vermis is indicated at P4 in a thin layer of fibrillary tissue (indicated by small bubbles) which forms part of the roof of the forth ventricle. R. nystagmus disappeared a few days after surgery. During the terminal examination several years later, R. nystagmus in the dark was noticed. Furthermore, pursuit eye movements were typically too slow and had to be

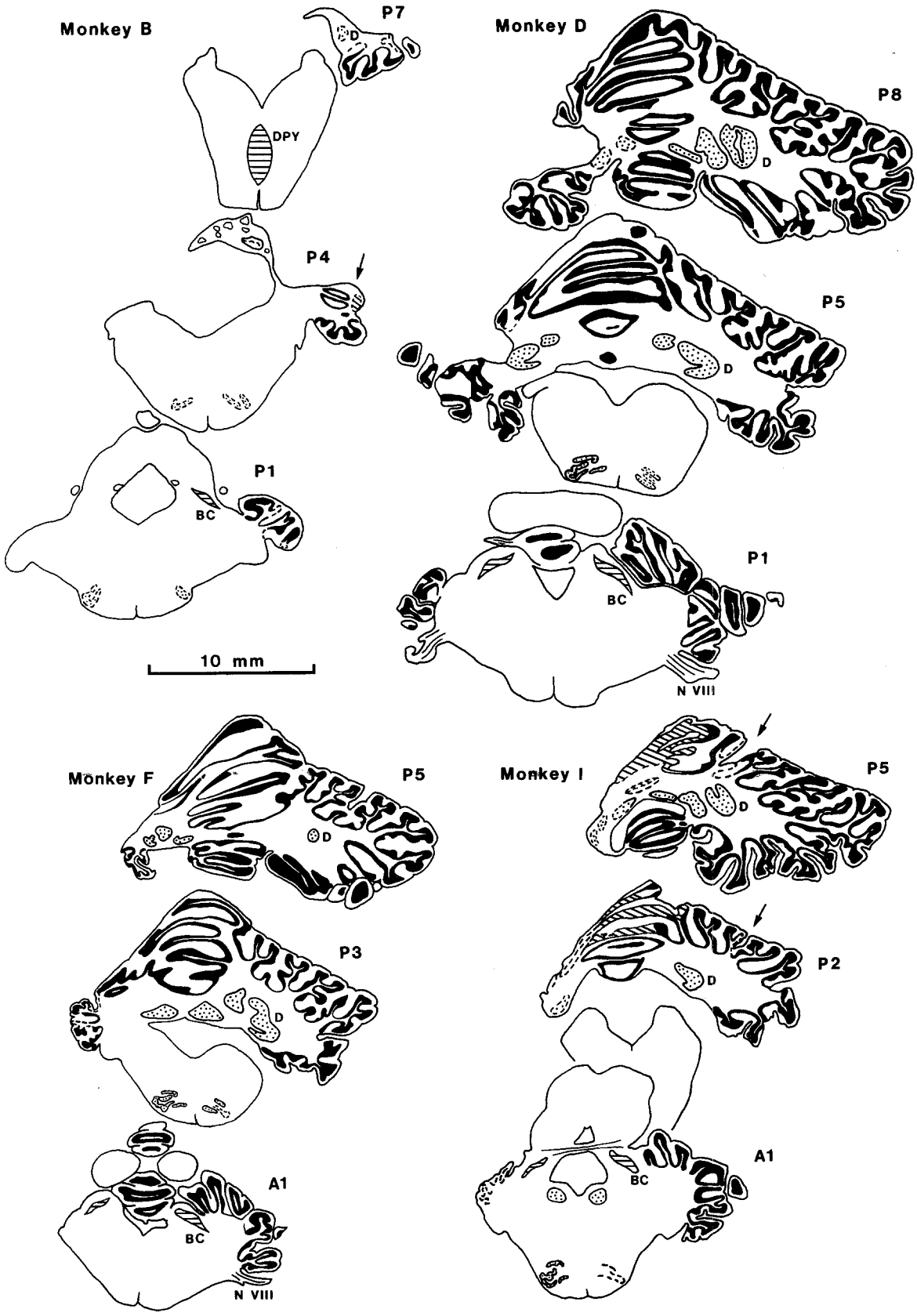

Fig. 2. Semi-schematic drawings of frontal sections through the cerebellum of monkeys B, D, F, and I, demonstrating the extent of cerebellum lesions. For each monkey, the sections represent three different planes, about 3 mm apart

augmented by saccades. Gaze holding failure in the far right field, as well as polysaccadia were also observed.

Movements in the cage were slightly reduced in speed and exhibited ataxia. The animal seemed to be more withdrawn and less inventive than normal monkeys. A cerebellar defect could be suspected from observation of its motor performance.

Monkey D. Macaca arctoides, female, age 4 years, weight: 5.6 kg; brain weight after perfusion: 110 g. Cerebellar ablation within the first week after birth included the right hemisphere and part of the vermis but essentially spared the nuclei. BC was clearly smaller (at P1) on the right than on the left side as could be expected from the asymmetric cerebellar loss. At P5 and P8 the lesion touched and even reached into the right dentate nucleus (Table 1).

During the first post-operative weeks both eyes stayed within the left hemifield. Pursuit eye movements to the left were initially impaired but recovered within a few months. No residual oculomotor deficits existed several years later. Motor performance, which was examined in the cage and in the primate chair during long training sessions demanding quick hand responses to moving visual stimuli, showed no detectable signs of any deficits.

Monkey F. Macaca fascicularis, female, age 4 years, body weight: 2.6 kg; brain weight after perfusion; 63 g. Cerebellar ablation within the second week after birth included the right hemisphere and most of the right paraflocculus and flocculus but spared the nuclei. The BC (lower left in Fig. 2) at A1 was considerably smaller on the lesioned side. Atrophic areas in the unlesioned rudiment of the right flocculus and paraflocculus are indicated by broken lines at P3. Signs of initial oculomotor deficits were quite similar to those of monkey D. Again, no oculomotor defects could be detected several years later.

Motor performance in the cage and during training sessions in the primate chair was quite normal.

Monkey I. Macaca fascicularis, female, age 5, body weight: 4.3 kg, brain weight after perfusion: 60 g. Cerebellar ablation was performed nine months after birth. The ablation included the right hemisphere as well as the right paraflocculus and flocculus but spared the nuclei. Parts of the vermis were also lesioned as judged from signs of surface degeneration at the time of perfusion. The status of the remaining cerebellar portions is remarkable in several respects: large portions of the vermis were severely atrophic: arrows at P2 and P5 indicate a region in Crus 1 of the right neocerebellum with severe cortical atrophy, which was clearly distant from the initially lesioned part (see: Discussion).

After the surgery both eyes stayed in the left hemifield, and smooth eye movements to the right were impaired. In addition, truncal ataxia occurred which improved slightly in the first postoperative months. During the terminal examination the monkey exhibited polysaccadia and gaze holding failure in both extreme horizontal fields, as well as R. nystagmus in the dark. Barany tests revealed that postrotatory nystagmus in the light lasted longer (about 20 s) after left rotation than after right rotation (only about 7 s). Trained foveal pursuit showed a clear deficit. Motor performance seemed inconspicuously normal except for a head tremor. This judgment holds for examinations in the cage and the chair.

The vestibular nuclear complex appeared normal on both sides only in monkey D. In the other brains a reduction was particularly clear for the nucleus vestibularis lateralis (Deiters) on the right side as could be expected from lesion of the ipsilateral flocculus.

Note that the brains of monkeys B and D (both Macaca arctoides) have a slightly different stereotaxic layout than those of monkeys F and I (Macaca fascicularis).

II. Neuroanatomical changes in the brain stem

The brain stem, which has manifold direct neural connections to and from the cerebellum, was examined for signs of neuroanatomical changes. Table 2 gives the summarized results of this qualitative light-microscopic screening which focused on main precerebellar nuclei as well as those efferent to the cerebellum. Some other nuclei with less prominent direct cerebellar connections (see: Brodal 1981) were not considered here. In addition, the substantia nigra (SN) was examined.

A. Precerebellar nuclei

1. Inferior olivary complex. Among the subdivisions of inferior olivary complex (Bowman and Sladek 1973; Brodal 1981; Larsell and Jansen 1972) the principal olive (OIP) was found to be most severely effected in our cerebellectomized monkeys (Table 2). In monkey B, there was no trace of any cells in OIP on either side. In the monkeys with hemilateral ablations, degeneration was limited exclusively to the contralateral OIP (Table 2); the extent of degeneration was variable, depending on the amount of

Table 2. Neuroanatomical status of brain stem nuclei in monkeys with neonatal cerebellar ablation

Brain stem region	Abbreviation	Monkey B		Monkey D		Monkey F		Monkey I	
		L	R	L	R	L	R	L	R
A. Inferior Olivary Nuclei									
N. Olivaris inferior principalis	OIP	+++++	+++++	+++	N	++++	N	+++++	N
N. Olivaris inferior dorsalis	OID	++++	+++++	+	N	+	N	++++	+
N. Olivaris inferior medialis	OIM	+++++	++++	+	N	+	N	+++++	N
B. Pontine nuclei									
N. peduncularis	NP	+++++	++++	+++	N	++++	N	++++	N
V. ventralis	NV	+++++	++++	++	N	++++	N	++++	N
N. lateralis	NL	+++++	++++	++	N	+++	N	++++	N
N. dorsalis*	ND	+++++	++++	+	N	+	N	+	N
N. dorsolateralis	NDL	+++++	++++	++	N	++	N	++	N
N. parmedianus	NPM	+++++	++++	+	N	++	N	++	N
N. medianus	NM	+++++	+++++	+	N	+	N	+	N
C. Reticular nuclei									
N. reticularis tegmenti pontis	RTP	++++	++++	+	N	++	N	++	N
N. reticualris lateralis	RL	+++	+++	+	++	++	N	+	+++
D. Red Nucleus									
N. ruber pars magnocellularis	NRM	+	+	+	N	N	N	N	N
N. ruber pars parvocellularis	NRP	++	++	+	N	+++	N	++	N
E. Thalamus									
N. ventralis lateralis	VLA	+	+	N	N	+	N	+	N
F. Substantia nigra	SN	N	N	N	N	N	N	N	N

N, normal; +, slightly degenerated; ++, clearly degenerated; +++, strongly degenerated; ++++, almost completely degenerated; +++++, completely degenerated. L: left, contralateral to cerebellar ablation side; R: right, ipsilateral to ablation side. *, N. dorsalis, here referes to the dorsomedial group of cells

neocerebellar ablation. Thus, in monkey I, with complete hemilateral ablation, no trace of cells could be detected contralaterally in OIP; but in monkey D, islands of cells were found surviving in the contralateral OIP.

The accessory olivary nuclei showed a variable pattern of degeneration. Thus, in monkey B, both the dorsal (OID) and the medial (OIM) accessory olives exhibited severe cellular degeneration (Table 2). Only an island of cells, presumably part of the caudal aspect of right OID, was found to be intact. In monkey I, accessory nuclei were heavily degenerated contralaterally and lightly so ipsilaterally. However, in monkeys F and D, where the vermis was relatively intact, the accessory olives showed only partial signs of degeneration, including cell loss and volume reduction (mainly on the contralateral side) (Table 2). Based on the study of both fiber and cell sections, a clear reduction in the size of inferior cerebellar peduncle (corpus restiformis) could be detected contralaterally to the ablation side.

2. *Pontine nuclei.* The response of the pontine gray (Brodal 1979; Nyby and Jansen 1951; Sunderland 1940) to neonatal cerebellectomy showed some similarities and some differences when compared to the pattern of degeneration in the olivary nuclei. Thus, in accord with the pattern seen in the olivary nuclei all evidence of degeneration in the pontine nuclei was limited exclusively contralaterally to the ablation side (Table 2). However, in contrast with the olives, the extent of degeneration varied considerably among the animals, as well as among the individual pontine nuclei (Table 2). The most massive pontine degeneration was present in monkey B, where only a few small islands of large but palely staining cells had survived, scattered among the various nuclei. These cells were most likely related to cerebellum, because they were only found on the right side, contralaterally to the remaining parts of the flocculus and paraflocculus on the left side, with which the above cells had presumably maintained connections.

Among the monkeys with hemicerebellar ablation the most extensive pontine degeneration was found in monkey I, and the least in monkey D roughly in the same proportion as the extent of cerebellar ablation. The boundaries of the various

pontine nuclei are poorly defined (Brodal 1981; Larsell and Jansen 1972), making judgments about the exact localization of degeneration rather difficult. Nevertheless, based on the information available in literature (Brodal 1979; Nyby and Jansen 1951; Sunderland 1940), it may be stated that in our hemilateral monkeys (Table 2), of all the nuclei of pontine gray, contralaterally to the ablation side, the nucleus peduncularis (NP) was most severely degenerated, followed by nucleus ventralis (NV) and nucleus lateralis (NL). The nucleus dorsolateralis (NDL), paramedian (NPM), median (NM) and dorsalis (ND) were less affected. Nucleus dorsalis here refers to the dorsomedial cell group in the pontine gray. In fact most of the true dorsal area is taken up by nucleus peduncularis (see Nyby and Jansen 1951). It must be stressed that even in the less affected nuclei, there was no question of some cell loss and small to moderate reductions in the nuclear size. Interestingly, the anterior aspects of the pontine complex were found to be more extensively degenerated.

An additional and clear finding in relation to the pontine degeneration was the massive reduction in the size of brachium pontis ipsilaterally to the ablation, easily visible on the lateral and ventral aspects of the intact pontine nuclei. In monkey B, the marked reduction in the size of brachium pontis was bilateral. These reductions in size were also evident in fiber stained sections by comparison of the middle cerebellar peduncle on both sides. Here, the size reductions were observed contralaterally to the ablation side.

3. Reticular nuclei. Two precerebellar reticular nuclei were included in our examination, nucleus reticularis tegmenti pontis (RTP) (Brodal 1956; Brodal 1980; Brodal 1981), situated dorsally to the pontine nuclei, and nucleus reticularis lateralis (RL) (Blakeslee et al. 1938; Brodal 1981), situated in the medulla, dorsolaterally and caudally to the inferior olivary complex. In monkey B, RTP was found to be completely degenerated except for the presence of a few large cells scattered throughout the presumed location (Table 2). Among the hemicerebellectomized cases, the RTP ipsilateral to the ablation was found to be essentially normal (Table 2). However, similarly to the medial group of pontine nuclei situated just underneath it, the contralateral RTP showed moderate but clear evidence of reduction in nuclear size and cellularity. The atrophy was often limited to the more lateral borders of the nucleus. In general, monkey D showed the least damage (Table 2), while F and I (Table 2) exhibited about the same reductions.

The RL of monkey B showed the heaviest extent of cell loss and atrophy, bilaterally. Interestingly, among the hemiablated monkeys a clear lateral pattern of degeneration was not evident. Thus, in both monkeys D, and I the reduction in cell number and nuclear size was evident mostly ipsilaterally to the ablation side. In monkey I, extensive cell loss was found in the caudal magnocellularis segment, while the more rostral parvocellularis part of the nucleus showed more shrinkage than cell loss. In monkey F, however, the reduction in size and cellularity, though limited to the pars magnocellularis, was found contralaterally to the ablated part of the cerebellum.

B. Efferent connections of the cerebellar nuclei

Of these nuclei, the two main ones, i.e., nucleus ruber (NR) and ventrolateral nucleus of thalamus (VLA), being the principal recipients of afferent fibers from nucleus dentatus and nucleus interpositus (Brodal 1981; Carpenter 1956; Chan-Palay 1977; Larsell and Jansen 1972; Miller and Strominger 1977; Rand 1954) were studied. Examination of NR revealed an almost normal status in pars magnocellularis (NRM), with no evidence of cell loss; only in the case of monkey B (bilaterally) and D (contralaterally to the ablated half of cerebellum) was there some apparent reduction in cell size and neuropil (Table 2). In the more anteriorly situated pars parvocellularis of NR, (NRP), however, there were clear signs of degeneration, including reductions in cellularity and nuclear size (Table 2). The latter reductions in monkey B were evident bilaterally and in others contralaterally to the ablated side of cerebellum (Table 2). The most marked atrophic responses in pars parvocellularis were found in monkey F.

With regard to VLA, in monkey B the nucleus was found somewhat reduced bilaterally. A reduction in size was also evident in monkey I, contralaterally to the lesioned cerebellar hemisphere. In monkey F, some signs of cell loss were also apparent, contralaterally. But in monkey D, no clear sign of atrophy or degeneration was found.

III. Accessory findings

In addition to the examination of the above brain stem nuclei which are known to be directly on the input or output path of the cerebellum, a number of structures were also carefully examined which are associated with motor functions and have, in older clinical literature, been variously ascribed as showing

Table 3. Planimetry of motor cortex and pyramidal tract in monkeys with neonatal cerebellar ablations

	Monkey B		Monkey D		Monkey F		Monkey I	
	L	R	L	R	L	R	L	R
A. Cerebrum surface (mm^2)								
Area 4+6 at A13.5 (mm^2)			46.39	45.0	35.0	37.22		
Area 4+6 at A12.0 (mm^2)			50.28	49.17	28.06	25.56		
Area 4 at A10.5 (mm^2)			47.78	44.72	26.39	28.06		
Area 4 at A9.0 (mm^2)			43.89	42.36	22.08	22.64		
			A14.5–A7.75		A14.5–A9.0			
aver. surf. (4+6) (mm^2)			47.89	46.56	29.47	29.46		
av. surf. (4+6) diff. (%)			(L 2.86% > R)		(L 0.03% R)			
av. surf. (total cortex) (mm^2)			170.8	170.2	111.0	107.6		
av. surf. (hemisphere) (mm^2)			488.6	487.6	305.2	303.3		
B. Pyramidal Tract surface (mm^2)								
	at A1.0		at A2.0		at A2.0		at A2.0	
section level I (mm^2)	2.25	2.07	3.34	3.32	1.40	1.45	2.04	2.04
	at P1.0		at A1.0		at AP0.0		at A0.5	
section level II (mm^2)	2.38	2.28	2.97	2.94	1.25	1.22	1.92	1.65
	at P3.0		at AP0.0		at P2.0		at P1.0	
section level III (mm^2)	1.95	2.01	2.88	2.73	1.14	1.13	1.51	1.44
	at P5.0		at P1.0		at P4.0		at P2.5	
section level IV (mm^2)	1.99	1.96	2.59	2.61	1.20	1.15	1.92	1.79
	A2.5–P6.5		A2.5–P1.0		A3.0–P4.25		A3.5–P3.0	
average surface (mm^2)	2.24	2.18	2.99	2.94	1.22	1.24	2.09	2.02
av. surface diff (%)	(L 2.8% > R)		(L 1.7% > R)		(R 1.6% > L)		(L. 3.5% > R)	

compensatory hypertrophy in response to cerebellar maldevelopments (see Discussion). We therefore examined, by qualitative and quantitative methods, three of these structures, namely, substantia nigra (SN), motor cortex and pyramidal tracts.

A. Substantia nigra. Careful qualitative examination of serial sections of SN in all the monkeys revealed a normal appearance (excluding lateral displacement) of both pars compacta and pars diffusa of SN on both sides, with no consistent and obvious indication of lateral asymmetry or enlargement on any side (Table 2).

B. Morphometric studies on motor cortex and pyramidal tract. Every 20th section with cell stain (0.5 mm apart) in the anterior brain region between the stereotaxic coordinates A7 and A15 of monkey D and F was subjected to quantitative measurements of surface area of the cerebral cortex by means of planimetry (see: Methods). These sections comprise Brodmann's area 4 and parts of area 6, which had been implicated to play a major role in compensation of neocerebellar lesion in the adult animals (Aring and Fulton 1936; Carrea and Mettler 1947). The cerebral hemispheres were compared by surface measurements (average of five values with a measurement error of less than 1%) of the total hemisphere, the total cortex, and the cortex of individual gyri on the left versus right side. Also, the cell density and general appearance of the cortex were carefully compared on the left versus right side. No significant differences (except for local differences, because the pattern of sulci and gyri is not identical in both hemispheres) between cortical parts of the left versus right hemisphere were found to support the old indications of morphological signs of compensation in the clinical literature (see: Discussion).

Part A of Table 3 gives the surface values of the precentral motor cortex at four different frontal planes (A 13.5 to A 9.0) including the superior bank of the sulcus centralis and the superior bank of the sulcus cinguli (Bonin and Bailey 1947; Macpherson et al. 1982). Furthermore the average cortical surface of area 4 and part of area 6 was calculated for the sections from A 14.5 to A 7.75 in monkey D (average

of 14 values) and from A 14.5 to A 9.0 in monkey F (average of 12 values). The figures show that on the average the left part of the analyzed precentral cortex was larger than the right part by only 2.86% in monkey D and had about the same size in monkey F. For comparison the average surface of the total neocortex as well as of the total hemisphere was calculated for the same set of sections. Again these average values in Table 3 indicate no significant hemispherical differences, although being clearly different for the two monkeys.

The cross-sectional area of the pyramidal tract was also measured of every 10th section by means of planimetry covering a range of 7 mm in the brains of all four monkeys to compare the left versus right side. Typically, clear differences on a single section would level off in subsequent sections and eventually even reverse the trend. Therefore one could easily arrive at misleading conclusions without examination of serial sections.

Part B in Table 3 gives the surface values of the pyramidal tract at four different section levels (I to IV) which correspond to different frontal planes as indicated for each monkey individually. In three monkeys (B, D, F) there appeared to be no consistent differences between the two sides, but in monkey I the left pyramidal tract had an up to 17% larger cross sectional area than the right one, consistently over the 4 mm range were it was sectioned least obliquely. This clear asymmetry is also reflected in the percentage of average surface difference in the bottom line of Table 3 which was calculated from the average surface values for the whole set of sections. In contrast, the slightly larger average left pyramidal tract surface in monkey B is not consistent with the surface values at all individual section levels. Note, that the average pyramidal tract surface in monkey B with a body weight of 7.1 kg and clear signs of ataxia amounted to only about 2.2 mm^2 whereas the well compensated monkey D (same sub-species as monkey B) with a body weight of 5.6 kg had a considerably larger pyramidal tract surface of about 3 mm^2.

C. Lateral displacement. The neonatal removal of substantial amounts of cerebellar tissue obviously led to sizable distortions and displacement of the brain. The brain stem structures in particular appeared to be significantly displaced caudorostrally and twisted around the imaginary axis of the neural tube. This type of distortion was particularly evident in monkeys F and I, as demonstrated by our finding that brain stem nuclei such as the VI nerve nucleus or the inferior olive appeared in carefully aligned frontal sections about 0.5 mm further anterior on the left side than on the right side.

Discussion

I. General anatomical considerations

This study reports in some detail the neuroanatomical correlates of neonatal cerebellar ablations in monkeys. Previous investigations in this line using neonatal lesions had been carried out mainly in newborn rabbits and kittens (Brodal 1940). To be sure, several studies based on retrograde degenerations of fibers and cell bodies have been carried out in adult monkeys (see Brodal 1981; Larsell and Jansen 1972). In agreement with the results obtained in the adult monkeys, our study clearly indicates that neonatal ablation of cerebellum, even if limited to the cerebellar cortex, sparing the nuclei, also results in severe retrograde degeneration, and in some cases, complete loss of the cells in the two main projection nuclei, i.e., pars principalis of inferior olive and some of the pontine nuclei. Moreover, in both cases the latter degeneration was limited exclusively and clearly to the contralateral side. The occurrence of such massive degeneration in the brain of the newborn monkey indicates that in this animal, the projections from the cells of the inferior olive and pontine nuclei have, at birth, already reached their destinations in the cerebellum and are most likely operational. This concords with the relative maturity of cerebellar morphology and foliation as well as the relatively high degree of motor control seen in newborn monkeys (Howard 1973).

The relatively intact appearance of the accessory olives after hemilateral cortical lesion in monkeys F and D, where the lesion had spared the vermis, compared to the massively degenerated appearance of these nuclei in monkey I, where the lesion had included the vermis, provides further evidence for the view that in the monkey these primitive parts of the olivary complex are highly connected with the vermis.

The differential degenerative responses of pontine nuclei contralateral to the cortical ablation indicate that while some of nuclei – i.e., peduncular, lateral and ventral – have mainly contralateral connections with the cerebellar neocortex (therefore showing severe degeneration in monkeys D and F), the more medial group of nuclei probably have bilateral connections. Previous research using retrograde degeneration methods (Nyby and Jansen 1951; Sunderland 1940) as well as HRP tracing (Brodal 1979) have also indicated the presence of both contra- and bilateral pontocerebellar connections in the monkey.

The mild and contralateral pattern of degenerative responses of RTP in the hemilateral monkeys

can be explained either by the bilateral nature of the projection from RTP to the cerebellar cortex (Brodal 1980), or alternatively by the presence of direct projections from RTP to intracerebellar nuclei (Chan-Palay 1977).

Our findings in RL are more difficult to interpret. As with RTP, the most severe degeneration was found in monkey B, in agreement with the findings of Blakeslee et al. (1938) who reported complete degeneration and disappearance of RL cells in adult cerebellectomized monkeys. The lack of a clear pattern of degeneration in RL of our hemicerebellectomized monkeys may reflect partly the presence of bilateral projections from this nucleus in the monkey, as well as to the differential lesion patterns.

On the output side of the cerebellum, the observed degenerative responses in the red nucleus and VLA of thalamus after cerebellectomy are consistent with the results obtained in the adult monkeys (Miller and Strominger 1977; Rand 1954) as to the pattern of innervation of these nuclei by cerebellar nuclei and must be due mainly to transneuronal degeneration in response to the reduction or absence of the afferent influences from the dentate and interpositus, during the postnatal growth phase of the brain.

The relative sparing of the large cells of the NR in our hemilateral cases may result either from the corresponding sparing of nucleus interpositus – the principle source of cerebellar input to this portion of NR (Carpenter 1956; Miller and Strominger 1977) – or from the fact that these cells receive more inputs from other areas of CNS. Nevertheless, even these did not escape the transneuronal effects, as shown by the reductions in their size in monkeys D and B.

II. Are there morphological manifestations of compensation?

Since our monkeys exhibited a high degree of functional compensation which was virtually complete, if the intracerebellar nuclei had been spared (Eckmiller and Westheimer 1983) it seemed appropriate to examine the remaining cerebellum as well as the brain stem and neocortex for histological signs of compensation at the light microscopic level. Earlier experimental lesion studies in adult monkeys had implicated parts of the contralateral motor cortex in the compensation of cerebellar ablations (Aring and Fulton 1936; Carrea and Mettler 1947). Furthermore, various clinical case reports of human cases with severe cerebellar maldevelopments had described histological signs of enlargement of the contralateral neocortex (Anton 1903; Hitzig 1884; Vogt and Astwazaturow 1912), and the pyramidal tract (Anton 1903; Anton 1922; Stewart 1956). In contrast, our search for such signs of compensation by means of quantitative morphometry failed to reveal clear results, either in the cerebral neocortex or in the pyramidal tract (Table 3), or even in the remaining parts of the cerebellum. One possible explanation for the apparent difference between clinical reports of visible enlargements and our failure to find those may be that clear morphological signs of compensation for example in the cerebral cortex or pyramidal tract occur only if the cerebellar defect happened in an early embryonic stage rather than after birth. Presumably, the essential anatomic changes for functional compensation in our monkeys occur at a much smaller scale and could therefore be detected only by different and more specific methods (e.g. electron microscopy or modern neuroanatomical tracing methods). This view is in agreement with recent studies on this subject (Finger and Stein 1982; Flohr and Precht 1981; Kawaguchi and Yamamoto 1981; Leong 1977; Nicholls 1982; Van Hof 1981). Nevertheless, the mechanism of functional compensation of neonatal cerebellar ablations remains to be elucidated.

III. Histological abnormalities in the brain due to cerebellar defects in human cases

Numerous cases of congenital cerebellar maldevelopments, which incidentally are extremely rare in monkeys (see Innes and Saunders 1962), as well as cerebellar defects in early life or in childhood are described in the clinical literature (Blackwood and Corsellis 1976; Macchi and Bentivoglio 1977; Smith 1975). In addition, various atrophic changes of the cerebellum and its connecting pathways can occur throughout life (Dow and Moruzzi 1958). Among these are the olivopontocerebellar atrophies (Konigsmark and Weiner 1970), which are characterized by a loss of neurons in the cerebellar cortex, the pontine nuclei, and the inferior olive, and often become clinically manifest only in middle age. The abnormality pattern of these atrophies is particularly similar to that in our monkeys. Other brain stem nuclei were not systematically screened in the clinical reports. In contrast, several puzzling reports exist of young infants (one to two years old) with hypoplasia pontoneocerebellaris (Biemond 1955; Brouwer 1924). In these cases the inferior olives remained inexplicitly normal (or almost normal) whereas the neocerebellar cortices and the pontine nuclei were severely reduced. An earlier hypothesis (Brodal 1946), that the pontine nuclei or inferior olive are only effected

by a cerebellar lesion if their terminal fibers have already reached the cerebellum at the time of injury, might have offered an explanation. However, studies on chick embryos (Harkmark 1956) clearly demonstrated that secondary degeneration always occurs in normally developing pontine nuclei and inferior olive, once their axons reach the border of a previously performed cerebellar lesion.

In clinical reports of asymptomatic cerebellar maldevelopment, a reduction of the contralateral pontine nuclei and the contralateral inferior olive is described as the main abnormality pattern in the brain stem, as in olivopontocerebellar atrophies. In addition, some of these cases showed a reduction of the red nucleus (Anton 1903; Anton 1922; Erskine 1950; Rubinstein and Freeman 1940), and enlargement (Rubinstein and Freeman 1940) or reduction (Erskine 1950) of the substantia nigra, an enlargement of the contralateral neocortex (Anton 1903; Hitzig 1884; Vogt and Astwazaturow 1912), or even an enlargement of the contralateral pyramidal tract (Anton 1903; Anton 1922; Stewart 1956).

A cautious comparison of the described monkey brains with those of the clinical cases shows a common basic abnormality pattern in the brain stem: a clear reduction of the pontine nuclei and the inferior olive due to retrograde degeneration and some milder transneuronal degeneration in the red nucleus and VLA of thalamus, all contralateral to the effected part of the cerebellum. All other brain areas are less generally involved, suggesting a less direct dependence on the cerebellum.

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