AGE AND OTHER FACTORS IN MOTOR RECOVERY FROM PRECENTRAL LESIONS IN MONKEYS

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In man and in subhuman primates the paresis produced by lesions of the motor cortex is variable in respect of rate and of extent of ultimate recovery of motor power. Clinically various factors influencing recovery are recognized, such as the size and nature of the lesion and its location in the cerebral hemispheres, but the extent of recovery is generally unpredictable. In an experimental study these factors can be analyzed more precisely, and it is the purpose of this paper to present the results of such a study of the problem carried out on monkeys from which the various parts of the excitable motor regions of the cortex were extirpated. The regions removed were the motor and premotor areas, i.e., area 4 and area 6 a (upper part) of Vogt’s modification of Brodmann’s architectonic map of the cercopitheque brain (1, fig. 1). Following extirpation observations were made on the rate and degree of ultimate recovery of motor power. The effects produced by such lesions were found to differ strikingly in the infant monkeys from those seen in adult animals.

METHOD. During the past five years investigations of the functions of the frontal lobe of subhuman primates have been carried out at the Yale School of Medicine under the direction of Prof. J. F. Fulton (2, 3, 4, 5). The observations reported in this paper have therefore been made incidentally on a large number of animals operated upon by Doctor Fulton for other purposes, and, in addition, on a smaller number used specifically for this research. Motor pareses of one or more extremities were produced in monkeys of various species, in gibbons and in chimpanzees by total and subtotal ablations of the excitable regions of the frontal lobe. In 13 monkeys the motor and premotor regions were completely removed from both hemispheres (5).

Recovery of function was measured in several ways. The changes in activity of the deep reflexes of the lower extremities were noted, and, in the apes, the appearance of the pathological reflexes of the foot, the Babinski, Rossolimo, Chaddock and Oppenheim; the degree of resistance to passive manipulation (i.e., spasticity and flaccidity) and, with this, the presence or absence of reflex grasping, its time of appearance and disappearance, and its intensity were also observed. In addition the behaviour of the animals on the return of voluntary power was carefully studied;

1 This investigation was assisted by a grant from the Research Funds of the Yale University School of Medicine.
the phenomena ordinarily noted were: 1, movement at a given joint, shoulder, elbow, wrist, fingers, hip, knee, ankle and toes; 2, ability to use the extremity for support; 3, ability to use the extremity for walking and whether the dorsum of the foot or hand bore weight rather than the sole as in the normal animal; 4, ability to use the extremity in climbing; 5, prehension, i.e., use of the toes and fingers in picking up large and very small objects; 6, use of the operated extremity in voluntary motor performance as freely, as easily, and as often as the contralateral extremity.

In the 13 animals with bilateral extirpations, histological examination of the excised areas was made by Nissl’s method. The surrounding cortical tissue was also preserved at autopsy and regions adjacent to the lesion were similarly examined by Nissl technique. Special attention was paid to the presence or absence of the large pyramidal cells of Betz. In the series with bilateral extirpations the pre-motor area and all the motor area containing Betz cells was ultimately extirpated. In each instance in which the experiment was terminated within six weeks of the final lesions, the degeneration in cord and brain-stem were studied by Marchi’s method.

EXPERIMENTS. A. Extirpation of motor and premotor areas in adult and subadult monkeys. 1. Influence of the age of the animal. As the number of observations gradually increased it became evident that the age of the animals studied was an important factor in the ultimate degree of motor deficit. Thus adult monkeys from which motor and premotor areas had been removed from one side showed a greater degree of paresis immediately after operation and slower recovery of power than did adolescent or very young animals after the same procedure. The degree of ultimate recovery was also greater in the younger than in the older animals.

2. Influence of size of lesion (unilateral). The size of the lesion, as is well known in man, also affects the rate of recovery; being always more rapid after a small lesion than after a large one. Thus, if the entire motor area, i.e., the representation of foot, leg and trunk, as well as arm, was extirpated at one time, the rate of recovery of function in the hand and arm was slower than after ablation of the hand and arm area alone. Similarly, extirpation of either the motor or premotor area alone was followed by more rapid and more complete recovery than that following the simultaneous extirpation of both these regions. The influence of size of lesion applied only within the motor and premotor areas. Extirpation of the frontal regions anterior to areas 4 and 6, was performed without increasing the motor deficit. In three cases one entire hemisphere was removed. The ultimate motor deficit in such animals was no greater than that following ablation of motor and premotor areas alone.

3. Influence of the ipsilateral hemisphere. The motor and premotor areas in the ipsilateral hemisphere also influence recovery of power. Thus, if an animal from which the excitable motor area of one hemisphere has been removed, is allowed to survive several weeks or months, the motor deficit in the contralateral extremities gradually diminishes, until a permanent level is reached, at which time the animal shows a certain amount of power and
skill on the affected side. If then the corresponding motor area is removed from the second hemisphere, in addition to the deficit which appears in the side contralateral to this second operation, there is marked increase in the deficit of the ipsilateral side as well (12).

4. Influence of interval between ablations from opposite hemispheres. Bieber and Fulton (5) found that when the motor and premotor areas were removed bilaterally from adult monkeys the animals never recovered voluntary power. Such animals exhibited only certain involuntary movements and the rhythmic progressive movements of the “thalamic” monkey. They were entirely unable to feed themselves and remained lying on one side in characteristic postures (fig. 1) throughout the remainder of their lives. The animals studied by Bieber and Fulton were adolescent or young adult macaques (aged 2 to 4 years). They were operated on in two stages, the motor and premotor areas of one side were removed at one operation, and, in the majority of animals, the corresponding area was removed from the second side within two to three weeks.

In the present series of experiments it was found that a slight degree of voluntary power might return, even in adult animals, if the interval between the operations on the two hemispheres were greater than three to four weeks (see table 1). In the majority of animals motor and premotor areas were removed simultaneously from one side at a single operation (the left being the side of primary operation in all cases). The interval between
operations in the various experiments can be seen in the table. Seven instances occurred of recovery of some degree of voluntary power on the right side, and recovery occurred only in the animals in which a time interval of more than four weeks had elapsed between operations. Performance three weeks after the extirpation of the motor and premotor area from one hemisphere was usually maximal for the operated extremities, the gradual improvement in power having ceased. Except in two instances the recovery was seen on the right side only, i.e., on the side in which, because of a long interval between operations there had been a maximal recovery of voluntary power. Two cases showed some voluntary movement on the left or more recently operated side, as well as on the right.

**TABLE 1**

*Showing ultimate paresis of voluntary movement in bilateral motor and premotor preparations*

The series is listed in order of the time interval between operations. Those animals with short time interval show complete paresis and those with long time interval show incomplete paresis.

<table>
<thead>
<tr>
<th>SERIES NUMBER</th>
<th>INTERVAL BETWEEN OPERATIONS</th>
<th>FINAL DEGREE OF PARESIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Left extremities</td>
</tr>
<tr>
<td>Young or mature animals:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premotor ................</td>
<td>22</td>
<td>4 days</td>
</tr>
<tr>
<td>Premotor ................</td>
<td>16</td>
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</tr>
<tr>
<td>Premotor ................</td>
<td>15</td>
<td>17 days</td>
</tr>
<tr>
<td>Area 6 ................</td>
<td>1</td>
<td>35 days</td>
</tr>
<tr>
<td>Premotor ................</td>
<td>8</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Premotor ................</td>
<td>20</td>
<td>6 weeks</td>
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<tr>
<td>Premotor ................</td>
<td>30</td>
<td>2 months</td>
</tr>
<tr>
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<td>39</td>
<td>2 months</td>
</tr>
<tr>
<td>Premotor ................</td>
<td>24</td>
<td>3 months</td>
</tr>
<tr>
<td>Premotor ................</td>
<td>4</td>
<td>3 months</td>
</tr>
</tbody>
</table>

Voluntary power was never more than minimal in these older animals. It consisted solely in a response of an extremity in performing a purposeful movement. Some animals were able to propel a bit of food along the floor towards their mouths with their hands, others could awkwardly grasp the food and transfer it to their mouths. Most were able to right themselves, a few could stand, and one (premotor 4) in which a period of 15 weeks had elapsed between operations, was able to progress in an awkward fashion. None of these animals was in any way capable of caring for itself. Those in which the motor representation for the face area had been left could chew and swallow food which was placed in their mouths.

**B. Extirpation of motor and premotor areas in infant monkeys.** Because
of the extreme character of the deficit in older animals, the effect of similar lesions in very young animals was next investigated. The youngest animals previously studied were at least two years of age. Through the courtesy of Dr. Gertrude van Wagenen of the Yale Department of Obstetrics and Gynecology several new-born infant macaques (Macaca mulatta and Macaca irus) were made available. Infant monkeys at this age show many of the reactions seen in older animals after ablation of the excitable areas. Motor progression is awkward and forced grasping (fig. 2) is very pronounced (8). They exhibit changes in intensity of the reflex grasp on changing position, similar to those seen in the older animals after bilateral extirpation of the motor areas (5). Thus with the animal in the lateral position, the undermost extremities are extended, the uppermost are flexed and exhibit reflex grasping. Reversal of the position of the animal to the opposite side results in reversal of the postural pattern.

1. Unilateral lesions. a. Motor and premotor. From such an animal (premotor 28) at the age of 10 days the left motor and premotor areas were removed. The immediate recovery after the operation was surprising. Within 24 hours the animal walked about, using all four extremities, with only a slight lag in those of the right side. In purposeful movement, as grasping or picking up an object, the right fingers and toes were used less frequently and a trifle more awkwardly than the left, but even this disability disappeared within ten days. Forced grasping, after the first day when the right hand and foot showed weakness, was at all times equal on the two sides. It disappeared gradually during the second month of life and simultaneously on the two sides of the body. This animal then developed at a normal rate for a healthy infant and showed no motor deficit.

b. Entire hemisphere. A second infant (premotor 42) was operated on at the age of 40 days. From it the entire left hemisphere was removed. On recovery from anesthesia, during the first day after the operation, it showed the characteristic deficit of an adult animal after extirpation of a hemisphere: hemianopsia, loss of sensibility and motor paresis were present on the contralateral side. An adult during several weeks after hemispherectomy gradually recovers the use of the operated extremities for motor progression, but gross incoordination is present and ability to perform fine movements is permanently lost.

In this infant, recovery after twenty-four hours was as great as after several weeks in the adult. When returned to its mother at the end of forty-eight hours it clung with all four hands and feet in the position of the normal infant. Again, as with the previous infant, the rapidity and degree of recovery of motor function was surprising. No determinations of the recovery of sensory function could be made. At the end of a week the animal walked and climbed. At the end of a month it moved accurately and rapidly, using both hands and both feet equally; the right hand and
foot, however, were somewhat less accurate than the left. Forced grasping disappeared at the same time on the two sides. Four months after operation only a slight exaggeration and awkwardness of the movements of the right side distinguished this animal from a normal infant.

2. Bilateral motor and premotor. The motor and premotor areas were later removed from the second hemisphere of the first-mentioned infant at the age of five months (first operation when 10 days old). The recovery of voluntary power was immediate. Within a few hours of operation the animal showed the postural characteristics of the bilateral motor-premotor animal of Bieber and Fulton (5). It lay on one side with undermost limbs extended and uppermost flexed, reflex grasping appeared strongly in all four extremities and was to change in intensity with change in position of the animal. From the first day it was able to right itself when lying on either side and also to reach for and grasp objects voluntarily with the right extremities. After several days it could perform voluntary movements on the left side also and recovery thereafter was extraordinarily rapid and complete.

At the end of the first week after operation it could walk and climb and feed itself by approximating its mouth to the food rather than by using its hands. It climbed rapidly and fairly accurately, sometimes slipping on flat surfaces, and always progressing on a broad base; there was hypermetria and movements were less well performed on the left. At the end of one month the difference between the two sides had about disappeared and there had been great improvement in the skill and accuracy of movements. The animal now fed itself with its hands, climbing continued to be executed better than walking, and while the intensity of forced grasping had diminished, the tendency to climb and cling persisted. It was sometimes unable to detach itself from the bars of the cage and would cling for hours if not removed.

During the next four months the animal had grown and developed in a healthy normal fashion. Its motor performance had become so adequate that it might easily have passed for normal. However, a definite motor deficit was still present, and movements were slower than normal; when placed in a cage with two slightly smaller animals it was unable to hold its own with the more agile cage-mates. The walking movements were still hypermetric and the animal developed a gallop, which was like the hopping of a rabbit. There was no evidence of forced grasping, except that the animal clung for hours to the breast of a larger monkey in the manner of the new-born infant. It exhibited the usual curiosity of the monkey, running and climbing everywhere when set free in a room. It climbed awkwardly and in jumping from chair to desk, a distance of perhaps 5 feet, it frequently missed its aim and fell to the floor. High stepping and hyperextension of the extremities were also present, although on passive manipu-
lation rigidity was not noticeable. The animal is still alive, 18 months after its last operation, and its neurological condition is unchanged (see fig. 3).

**Discussion.** That the recovery of motor function after extirpation of excitable motor areas in these monkeys is influenced by the remaining cortical areas is consistent with the observations of numerous earlier investigators who have affirmed the presence of an influence from various contralateral and ipsilateral cortical motor areas. Foerster (10) has shown in human beings that, after destruction of the precentral cortex, there is recovery of voluntary motor power which is integrated by extrapyramidal cortical areas of the same hemisphere. He also demonstrated the influence of the hemisphere ipsilateral to the paresis in a case in which a degree of voluntary movement was restored to the hemiplegic fingers, but occurred only with simultaneous movements of the normal hand. Gardiner (9) reports the case of a woman who, after the removal of an entire hemisphere, was able to move the contralateral lower extremity. Wertheimer and LePage (6) have shown in dogs, and Fulton (7) in monkeys and chimpanzees, that lesions of one hemisphere affect the ipsilateral as well as the contralateral extremities. These facts are consistent with the presence of ipsilateral fibers found in the pyramidal tracts. The fact that in older adult monkeys a greater permanent deficit is maintained than in younger individuals might also be expected since it is known clinically that younger people and especially children, recover more quickly than adults from hemiplegias.

The ability of one cortical area to assume the integration of voluntary motor activity to a greater or less degree after destruction of another motor area normally responsible for such integration seems, thus, well established. However, Jacobsen (11) working on psychological tests with these same animals, and with others from which only the frontal areas had been extirpated, has found that there are functions which, unlike voluntary purposeful movement, can be entirely and permanently abolished by extirpations limited to all the frontal association areas. The faculty of immediate recall, that is, the ability of an animal to make a correct choice after a given time interval which is normally present in the monkey, is, after extirpation of all of both frontal areas, entirely and permanently lost, both in infants and in adult animals.

The faculty of immediate recall can, then, be integrated only in one specific cortical area, but the function of voluntary purposeful movement, most perfectly integrated in area 4, can be imperfectly assumed by other cortical areas. In the older animals in which motor performance is normally integrated at cortical levels, interruption of all these pathways is followed by partial recovery of function which, although minimal, is present under certain conditions even after removal of all excitable cortex.
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In the infants voluntary motor control after extirpation of all excitable tissue is entirely adequate to maintain the existence of the individual.

The question of which centers assume control of movement in these infants becomes of paramount interest. For various reasons it seems possible that these functions are assumed at subcortical levels. Clinical and experimental evidence indicates that subcortical centers,—the striate bodies, the cerebellum, influence motor performance. In the infant monkeys the pyramidal tracts are not yet developed and the relatively simple and uncoördinated movements of the animal at this age are, therefore, also integrated at a subcortical level. At such a time, then, unilateral and even bilateral removal of the excitable areas of the cortex can have little effect on motor performance, and the lower centers, functioning normally at this time, are able, as the animal matures, to integrate a remarkably accurate and well coördinated motor performance.

SUMMARY

Recovery of motor power in the extremities of monkeys after unilateral and bilateral ablations of the motor and premotor areas of the cortex, is influenced by a number of factors.

1. The age of the animals affects both rate of recovery and degree of motor deficit. Young and immature animals recover more quickly and extensively than adults.

2. The size of the lesion made in a single hemisphere also affects recovery, which is much more rapid after smaller lesions even though the smaller extirpations may include all excitable motor tissue for a given extremity.

3. The hemisphere ipsilateral to the extremities also influences recovery since extirpation from the motor areas of this side cause additional ipsilateral deficit.

4. In older animals when the interval between successive ablations of the motor-premotor areas of the two hemispheres exceeds four weeks there is some recovery. This slight return of voluntary movement occurs on the side that was first paralyzed.

5. In infant monkeys operated upon when forced grasping is normally present and when motor performance is still poorly coördinated, removal of the premotor and motor areas of one side has little effect on motor performance.

6. In such an infant extirpation of the motor areas of the second hemisphere after complete recovery from the first operation produces a permanent deficit, but voluntary movements are adequately performed, so that the animal is able to maintain itself, and to grow and develop normally.

7. The motor performance of such an animal, when well-grown (two...
Years of age) resembles that of the infant macaque. Forced grasping persists and movements are slow and incoordinated.

REFERENCES