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PARTIAL PREFRONTAL LESIONS AND GO–NO GO SYMMETRICALLY REINFORCED DIFFERENTIATION TEST IN DOGS

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Abstract. The effects of partial bilateral lesions situated in the prefrontal region on go–no go differentiation with symmetrical reinforcement were investigated in dogs. Bilateral removals of proreal gyri and medial cortical surface involving pregenual, genual, precruciatal (XM), subcallosal or medial subproreal areas did not impair performance of this test. Very small cortical lesions of proreal areas located under presylvian fissure impaired transiently the differentiation. Removals of the orbital gyri to the presylvian fissure caused severe and long lasting impairment of this differentiation. It was concluded that the orbital areas situated on the lateral aspect of the hemisphere in dogs was responsible for correct performance of go–no go symmetrically reinforced differentiation task.

INTRODUCTION

In a number of papers from this laboratory it has been established that the go–no go differentiation task with asymmetrical reinforcement was impaired after lessions sustained in various parts of the frontal lobes. Usually, the "go" responses were completely preserved and only the "no-go" responses were disinhibited. However, after some lesions both go and no–go responses were affected.

When the medial aspect of the prefrontal cortex limited to the pregenual gyrus and slightly encroaching upon XM areas were removed, the inhibitory conditioned reflexes (no-go) were impaired both in differentiation procedure (1, 2), and in conditioned inhibition procedure (9). Similar disorders were discovered after removal of anterior genual areas (3). On the other hand, if the lesions included XM and precruciate areas not only were inhibitory reflexes impaired, but also conditioned responses to the positive stimuli were disordered (7, 8).

When the lesions were sustained more dorsally, affecting only pro-

real gyri, the go–no go asymmetrical differentiation was not impaired when the intertrial intervals were as long as 60 sec, but they were impaired when these intervals were shorter (15 sec) (2).

Lateral prefrontal lesions encompassing the part of orbital areas extended up to the presylvian fissure, impaired the go–no go asymmetrical differentiation only with short intertrial intervals (15 sec), but this differentiation was not impaired when the intervals were long (60 sec) (2). In the conditioned inhibition procedure, which should be considered as a more difficult task, no-go responses were disinhibited even at the intertrial intervals of 1 or 2 min (9).

To sum up this data, it might be conclude that lesions sustained in the medial part of the prefrontal areas produced considerably stronger deficit of unreinforced no-go responses than lateral lesions.

Different results were obtained when the go–no go differentiation employed symmetrical reinforcement. The damage of the lateral aspect of the prefrontal cortex produced very large and long lasting impairment of this task, whereas lesions sustined in the medial part produced very slight or no impairment of this task (4, 5).

All of these results clearly show that the go–no go differentiation with asymmetrical and with symmetrical reinforcement are quite different tasks and depend on different structures.

The aim of this paper is to investigate in more detail prefrontal structures which are responsible for go–no go differentiation with symmetrical reinforcement.

MATERIAL AND EXPERIMENTAL PROCEDURE

Subjects. 27 naive mongrel dogs about 2 years old were used in the experiments. Dogs were randomly assigned to experimental groups for purposes of surgery. The first group (M) included eleven animals (dogs 1-8 and 17-19) in which medial prefrontal areas were intended for removal. Extent of these lesions was different in various dogs. The second group (L) included eight dogs (dogs 9-16) in which dorsolateral part of proreal gyrus and orbital gyri up to the presylvian fissure were removed. The third group (PL) included eight dogs in which partial lateral prefrontal lesions were made, in which following areas were ablated: dorsolateral and medial parts of proreal gyrus in dogs 20 and 21, area prorea situated under upper part of gyrus compositus in dogs 26 and 27, the orbital areas located under presylvian fissure (dogs 24 and 25), and orbital areas extended up to the presylvian fissure (dogs 22 and 23).

Surgical procedure. The Nembutal anesthesia was intraperitoneally administrated at 35 mg/kg of body weight. Following incision of the

dorsal surface of the scalp the bone superior to the frontal sinus was removed and the nasal openings were tightly packed with wax. A large removal of the bone overlying the prefrontal cortex was made. The dura was cut and retracted. The vessels on the cortical surface to be subjected to the removal were coagulated and then the lesions were made by suction with a fine aspirator. The dural edges were sutured and the scalp closed. All lesions were made under aseptic conditions. Following 7 days of recovery from surgery, the testing was continued until the preoperative criterion was reached.

Histology. After completing the test, the animals were anesthetized with Nembutal and perfused by heart with saline solution followed by 10% neutral formalin.

The brains were removed from the cranial cavity and kept in 10% neutral formalin solution for 4 to 6 weeks for further fixation. After fixation all brains were photographed, cut into blocks and embedded in paraffin. The 20μ frontal sections were cut serially. Every 10th section was stained alternately according to Nissl and Klüver–Barrera technique.

For detailed analysis of the extent of cortical damages the reconstructions were made in the following manner: every 20th frontal section was projected on the lateral, medial or horizontal surface of hemisphere depending on the place of lesion. To eliminate the differences in the shape

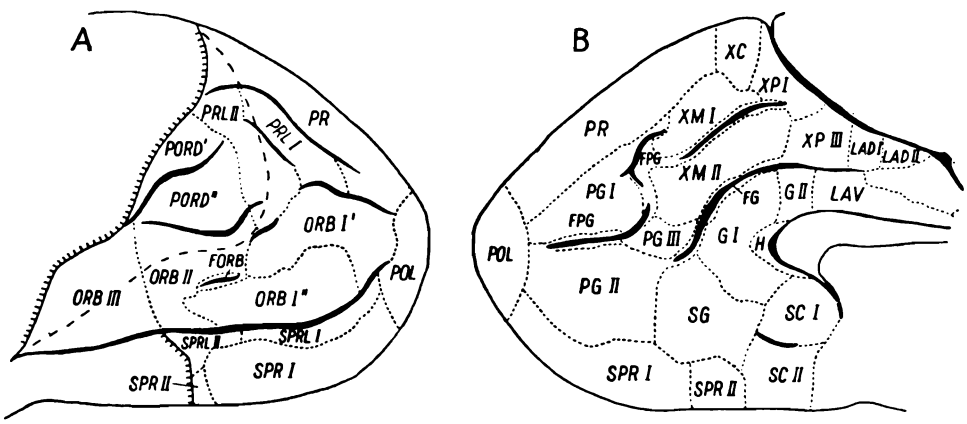

Fig. 1. The schemes of lateral (*A*) and medial (*B*) aspects of the dog hemisphere. (From Kreiner 1966.) Abbreviations; ORB I′, ORB I″, ORB II, ORB III, orbital areas; PG I, PG II, PG III, pregenual areas; POL, area polaris; PORD′, PORD″, paraorbital dorsal areas; PR, area prorea; PRL I, PRL II, proreal lateral areas; SPR I, SPR II, subproreal areas; SPRL I, SPRL II, lateral subproreal areas; FORB, orbital fissure; FPG, pregenual fissure; FG, genual fissure; XM I, XM II, medial precruciate areas; XC, area precruciata centralis; XP I, XP III, area precruciata posterior; SG, area subgenualis; SC I, SC II, subcallosal areas.

of dog brains and to facilitate the comparison of these lesions the results of reconstruction were next transfered on standard drawings according to Kreiner's patterns (6) (Fig. 1).

Since this study has shown the great importance of depth of the lesions for postoperative results, Figures have been labelled in the following manner:

1. Lined area indicates shallow damage not involving all the cortical layers.

2. Crossed area indicates damage in the whole thickness of the cortex involving sometimes some invasion of the white matter lying just below the cortex.

3. Black stain indicates deep damage of fibers in the white matter.

The reconstruction plates show the extent of lesions on the standard drawings of the frontal lobe and the frontal sections in the place of lesions.

Experimental procedure. The experiments were performed in a soundproof chamber. During preliminary training, an instrumental response of placing the right foreleg on the feeder during the stimulus (CS_1) was established by passive movements. Every response was reinforced by food (one small piece of bread soaked in meat soup). When the dog performed active movements to every stimulus during two consecutive daily sessions (20 stimuli a day), the differentiation procedure was introduced. One half of the dogs were trained with 15 sec intertrial intervals, while for the other half 60 sec intertrial intervals were used. Two tones 1000 cycle/sec (CS_1) and 700 cycle/sec (CS_2) were used as conditioned stimuli. When the dog performed the instrumental response during 5 sec presentation of CS_1, food was delivered and the stimulus sound was discontinued. During 5 sec presentation of CS_2, the dog was required to refrain from making the trained instrumental response and, if it did so, reward was given during the last second and then sound was discontinued. If the animal performed the movement to CS_2 or he did not make it to CS_1, the food was not delivered. Both stimuli were presented from one loudspeaker situated about 1.5 m in front of the dog. 20 stimuli (10 to CS_1 and 10 to CS_2) were presented in each experimental session in balanced order. The required criterion was 95% correct responses performed to both stimuli during 100 consecutive trials (5 days). When the dog reached criterion, an 8 day interval was imposed without training, and after this interval, the stabilization of criterion was checked during five consecutive sessions (100 trials). If the dog made more than five errors he was trained until he reached criterion again. But, if he did not make more than five errors, the training was terminated and the animal was subjected to the operation.

RESULTS

Figure 2 shows the effect of medial lesions on postoperative retention of differentiation. Criterial errors are included for comparison with the postoperative test scores. As we can see, dogs 1, 2, 5 and 8 were not impaired at all after operation, and dog 7 was almost not impaired, he

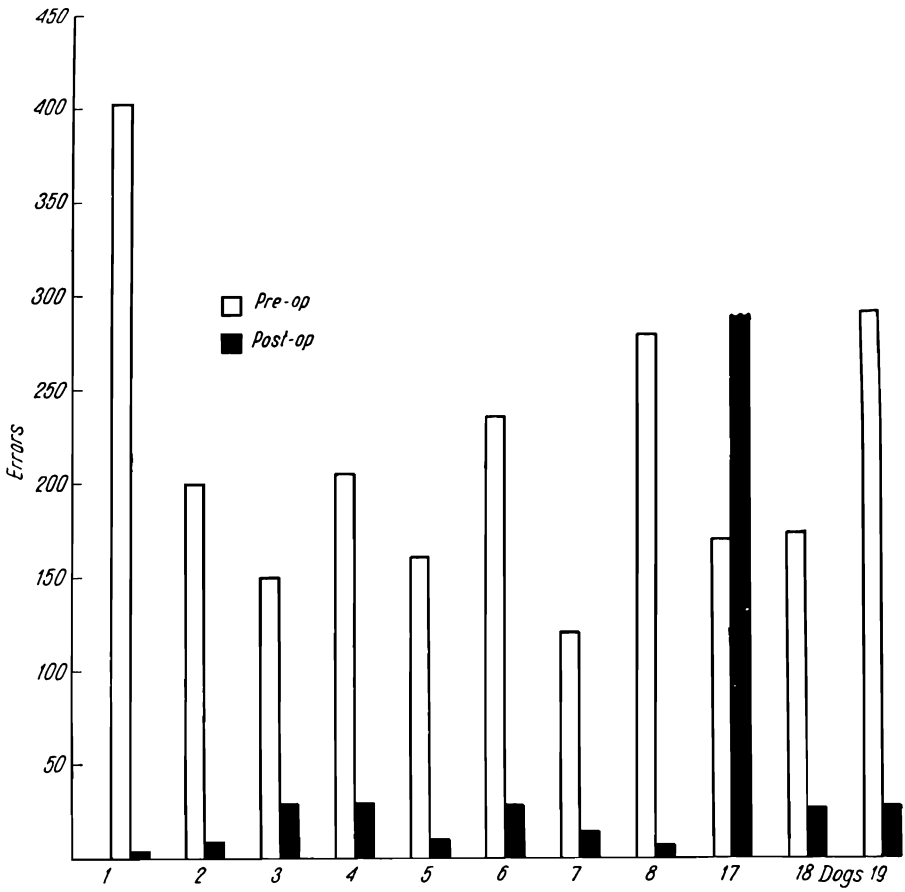

Fig. 2. Total number of errors made by each medial dog pre- and postoperatively. Empty columns, preoperative errors; black columns, postoperative errors.

made 14 errors after operation. Dogs 3, 4, 6, 18 and 19 were slightly impaired, requiring about 28 errors to reach criterion. However, dog 17 made many errors (291) postoperatively, much more than before operation, and he did not achieve criterion.

Histological verification of the brains (Fig. 3, 4 and 5) showed that in all dogs the proreal gyrus was affected. In dogs 1 and 8 it was almost

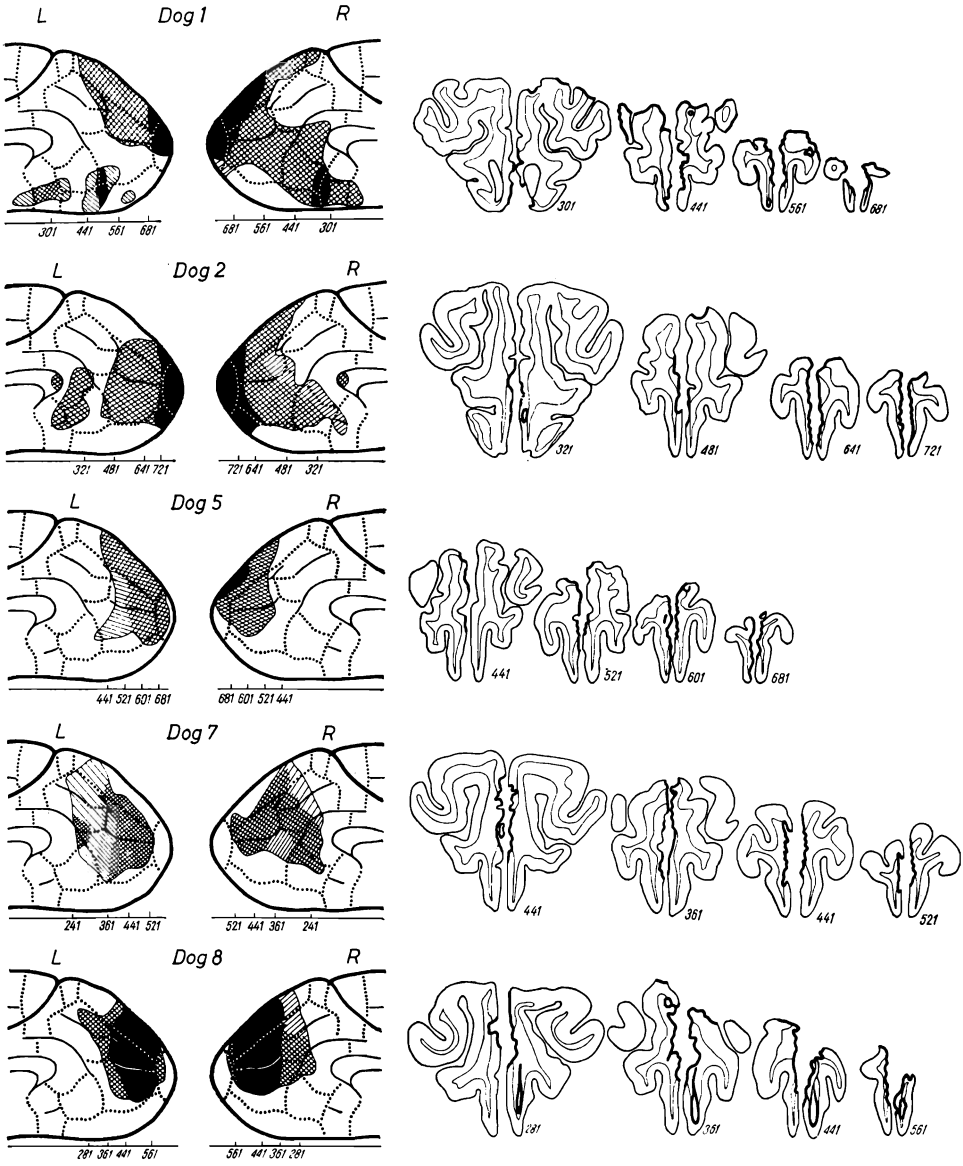

Fig. 3. Reconstruction of the medial lesions in dogs which were not impaired postoperatively in the differentiation test. Lined area shows shallow damage not involving all the cortical layers. Crossed area, damage in the whole thickeness of the cortex involving to some extent the white matter laying just below the cortex. Black stain shows the deep damage of fibers in the white matter.

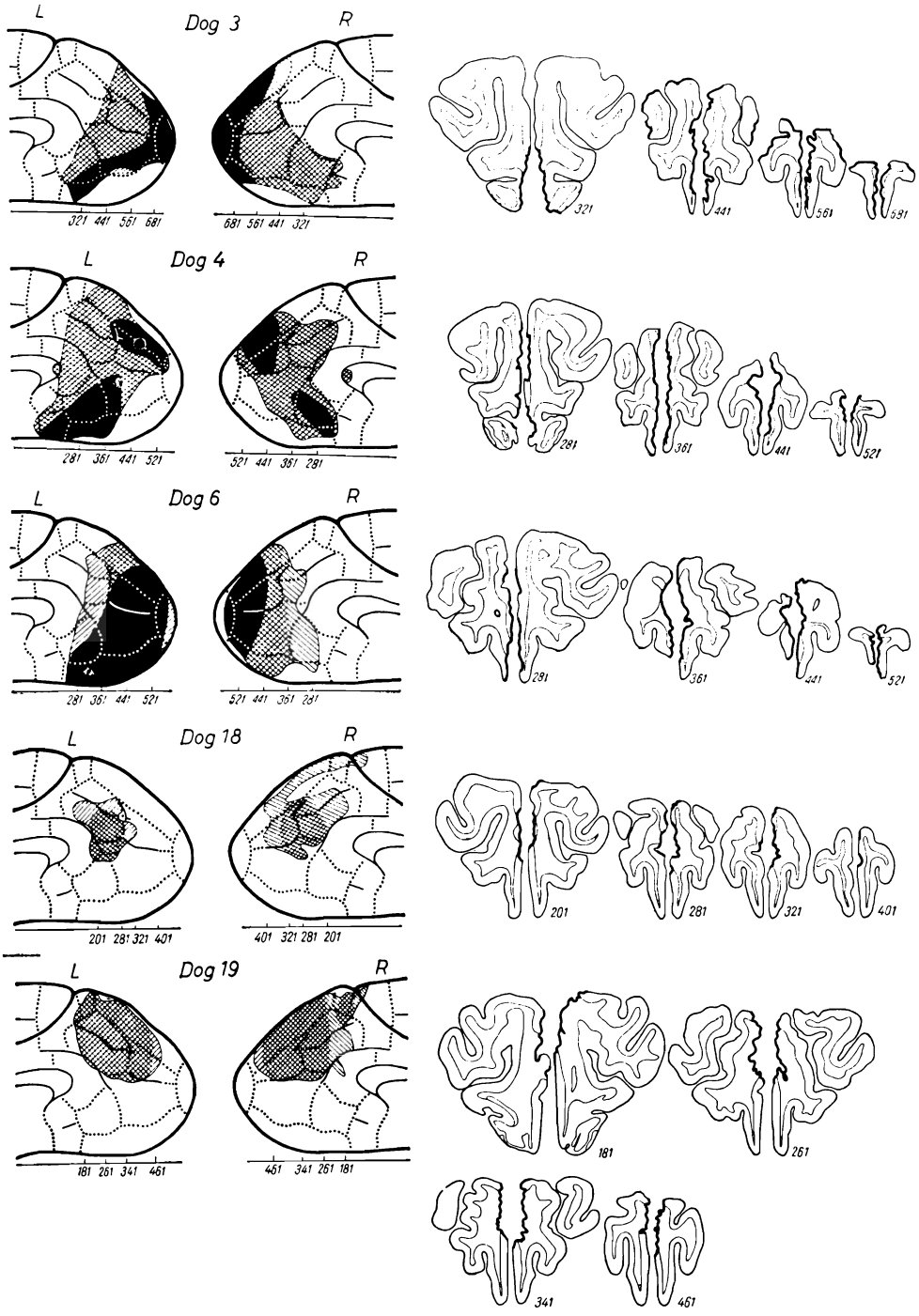

Fig. 4. Reconstruction of the medial lesions in the dogs which were slightly impaired in the differentiation test.

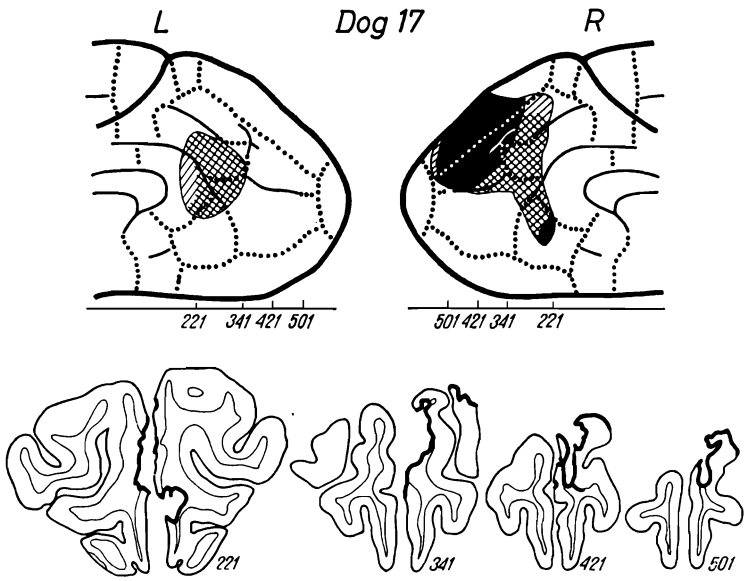

Fig. 5. Reconstruction of the medial lesion in dog 17 which was severely impaired in the test.

completely removed. Only the medial part of this area was removed together with some part of proreal fibers in dogs 2, 3, 4, 5 and 6. Only the medial cortical part of proreal gyrus was ablated in dogs 7, 17, 18 and 19. Pregenual gyrus I was completely ablated in dogs 1-8 and partially in dogs 17, 18 and 19. Pregenual gyrus II was removed completely or almost completely in dogs 2-8. In dog 18 this area was removed unilaterally only. Pregenual gyrus III was removed fully or partially in all dogs excluding dog 5. The largest removal of XM areas was in dogs 4, 18 and 19. Large but partial lesion of this area occurred in dogs 7 and 8. In the other dogs there were rather small partial lesions of this area. In few dogs there were very small unilateral or bilateral lesions in genual area (dogs 2, 4 and 7). Subgenual area was largely and bilaterally ablated in dogs 3 and 4, while in others (dogs 1, 2 and 6) rather small damages of this area were made. Subcallosal unilateral lesions were made in dogs 1 and 4. The medial part of subproreal gyrus was almost fully ablated in dog 6 and in dogs 1, 3 and 4 there was small damages of this area. The white matter located under the medial prefrontal areas was damaged to various extent in all dogs. Proreal fibres were largely removed in dogs 1-6 and 8. The fibers under the anterior part of the pregenual areas were damaged in dogs 1–4,6 and 8. Very small unilateral damage on the border of pregenual and XM areas occurred in dogs 1 and 7.

Also unilateral but deeper damage in this region than in dogs 1 and 7 was found in dog 6. There was bilateral but slight removal of the fibers on the border of pregenual and XM areas in dogs 3, 4, 6, 18 and 19 (Fig. 4); deep unilateral cut of fibers in this region was performed in only one dog 17 (Fig. 5). In the other hemisphere of dog 17 damage to the fibers in this region was slight.

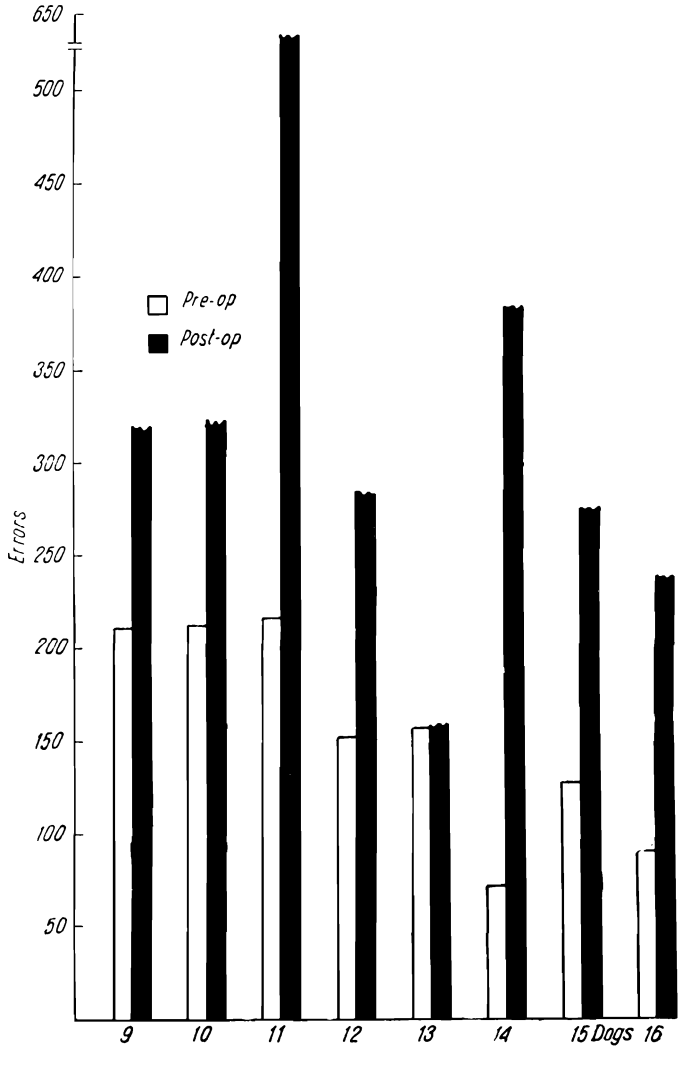

Fig. 6. Total number of errors made by lateral dogs pre- and postoperatively. Empty columns, preoperative errors; black columns, postoperative errors.

Figure 6 shows the effects of large lateral prefrontal lesions on retention of the symmetrical differentiation. Only 1 of 8 dogs reached criterion after operation. The others trained during various times even 1 year after operation could not achieve criterion. Postoperative training was interrupted when the dog had been trained for at least 800 trials and there was no tendency to decrease in the number of errors. Both the dogs trained with short and the others trained with long intertrial intervals were impaired after lateral prefrontal lesions.

As we can see in Fig. 7 the proreal lesion did not impair the retention of symmetrical differentiation test. The length of intertrial intervals did not influence the effect of this lesion.

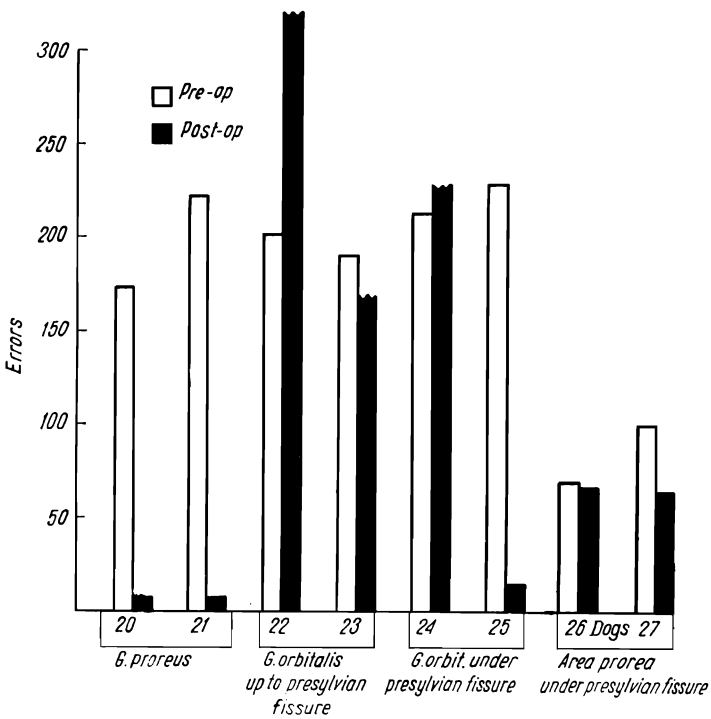

Fig. 7. Total number of errors made by dogs with partial lateral lesions. Empty columns, preoperative errors; black columns, postoperative errors.

Dogs 26 and 27, in which there was very small damage of the cortex limited to the area prorea located under presylvian fissure, were only moderately impaired in postoperative retention, and both of them reached criterion. They made 73 to 66 errors respectively.

The removal of orbital cortex to the presylvian fissure (dogs 22 and 23) produce very great impairment in retention, and these dogs could not reach criterion during 800 trials. The last dogs 24 and 25 in which the orbital area located under presylvian fissure was intended for removal showed no clear result. One of them, dog 25, made only 14 errors after operation. The second one, dog 24, did not reach criterion during 800 trials after operation and he made 227 errors. This dog was trained with 60 sec intertrial intervals while the training of the dog 25 used 15 sec intervals.

In all dogs of three groups the length of intertrial intervals did not affect the postoperative performance. Postoperative errors of these animals were made to the both conditioned stimuli.

Histological verification of lateral prefrontal lesions (Fig 8) showed that in all animals of this group the lesion involved dorsal and lateral part of proreal gyrus up to the presylvian fissure. Anterior part of orbital gyrus up to the presylvian fissure and dorsal part of area polaris were ablated too. Anterior parts of proreal and orbital gyri were removed together with their fibers. There is a possibility in these cases that the fibers running from anterior pregenual area were damaged. The dog 12 had unilateral deep damage of fibers in the orbital area. The extent of lesion in dog 13, which reached criterion postoperatively, was not smaller but as large as in other dogs of this group. In no dog was the posterior part of orbital gyrus III removed.

Histological verification of partial lateral prefrontal lesions (Fig. 9) reveals that the dorsal part of the proreal gyrus was removed fully and that the lateral part was partially damaged symmetrically in both hemispheres in dog 20. Fibers of the proreal gyri were damaged bilaterally. In dog 21 the dorsal part of proreus anterior was removed bilaterally. Posteriorly the borders of lesion are asymmetrical in the hemispheres. The lesion is larger in the left hemisphere than in the right one. The proreal fibers were cut bilaterally.

Removals of area prorea located under the presylvian fissure (Fig. 10) in dogs 26 and 27 were symmetrical in both hemispheres but the area precruciata was slightly damaged unilaterally in dog 27 and bilaterally in dog 26. Fibers in the posterior part of area prorea were slightly damaged in both dogs.

Orbital lesions (Fig. 11) in dogs 22 and 23 are not symmetrical. In dog 22 the lesion is larger in the left hemisphere and included the dorsal part of anterior orbital gyrus ORB I' and the anterior part of proreus lateralis PRL II. In the right hemisphere the lesion included the dorsal part of ORB I' and a small part of gyrus proreus lateralis. There was damage to the fibers in both hemispheres but in the left one this damage

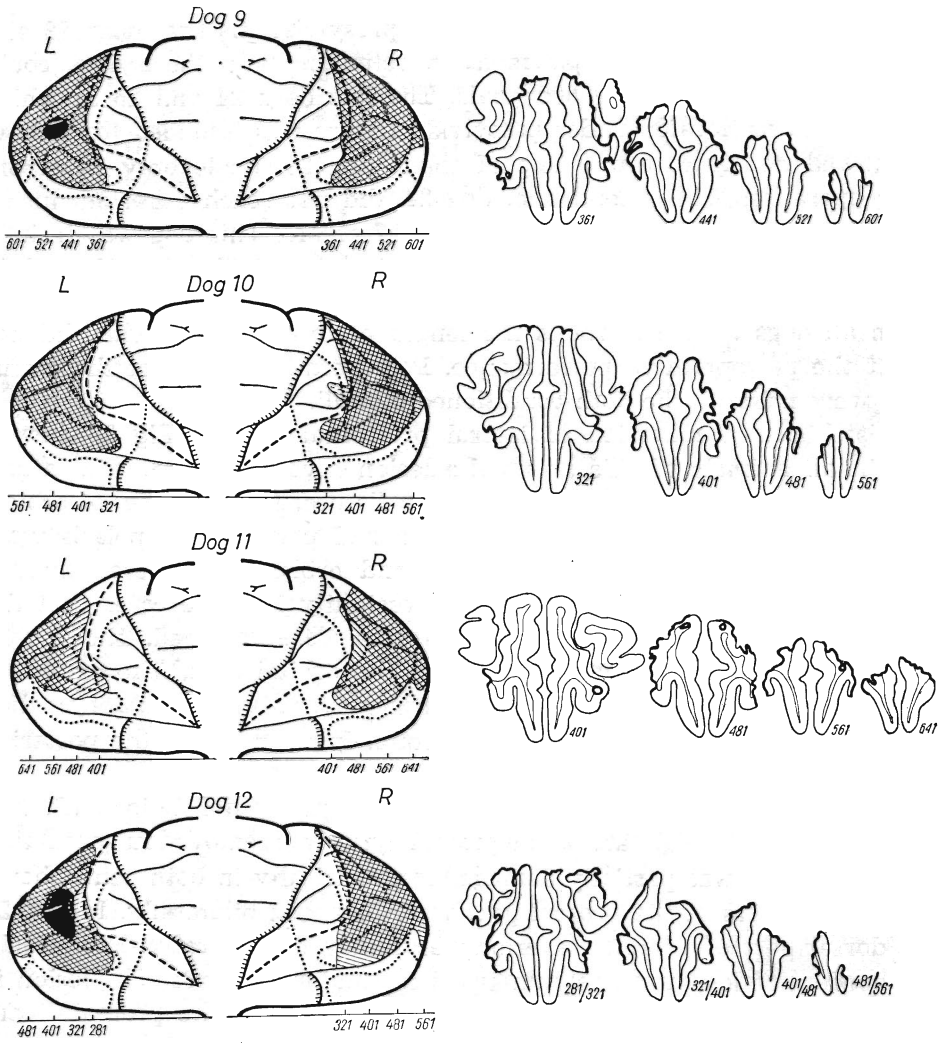

Fig. 8. For legends see opposite page.

was slight. In the right hemisphere, the removal was a little larger and limited to the orbital gyrus I'. The lesion in dog 23 was larger than in the previous dog. It removed bilaterally the anterior part of orbital gyrus (ORB I' and ORB I'') and the anterior part of gyrus proreus lateralis. In the right hemisphere the lesion extended more posteriorly to the ventral part of ORB II. The bilateral damage of the fibers was not deep and only orbital fibers were partially cut.

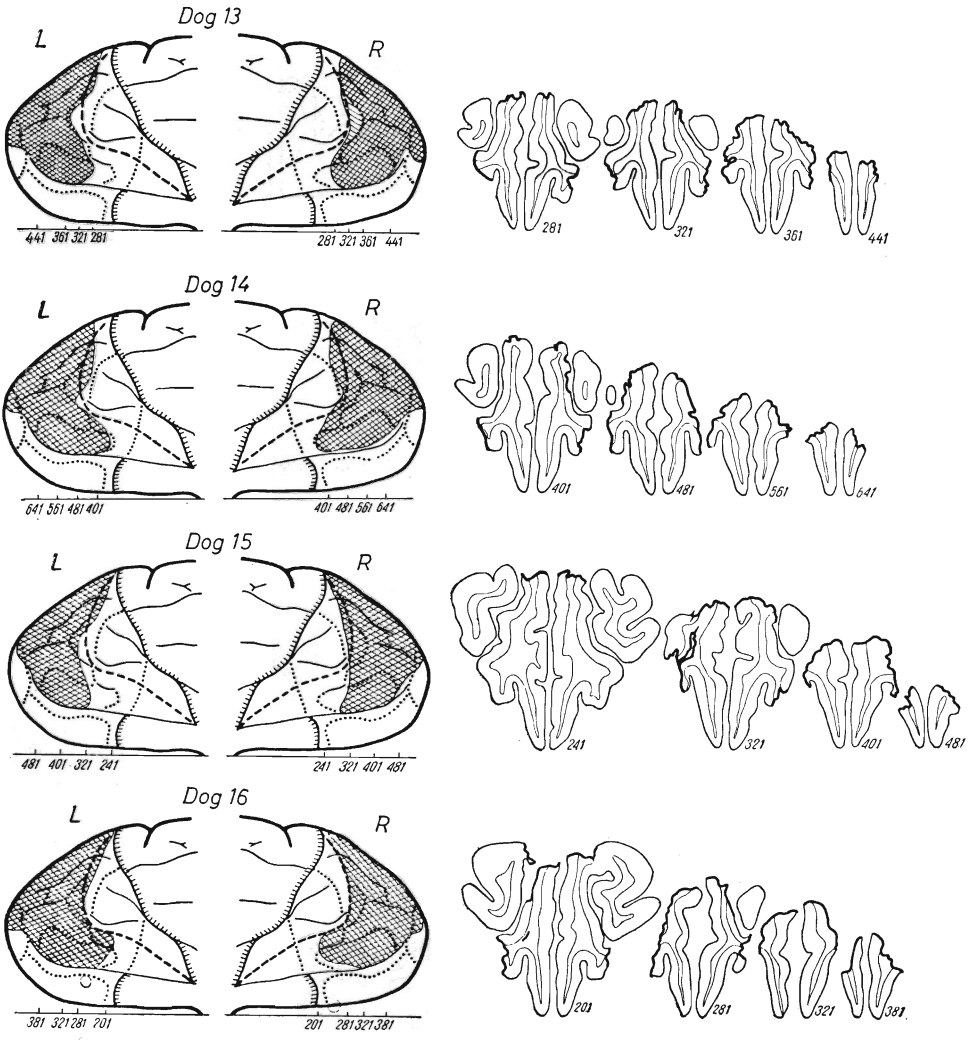

Fig. 8. Reconstruction of the large lateral lesions.

Removals of orbital areas located in the depth of presylvian fissure (Fig. 12) were not similar in the two operated dogs. In dog 24 the lesion was symmetrical and removed bilaterally gyrus proreus lateralis, the anterior part of area PORD, and a small part of ORB II, ORB I was almost not impaired. In the depth of presylvian fissure the fibers were damaged. These fibers were located between two cortical layers: anterior part of area PRL II and PORD" on the lateral aspect of the hemisphere

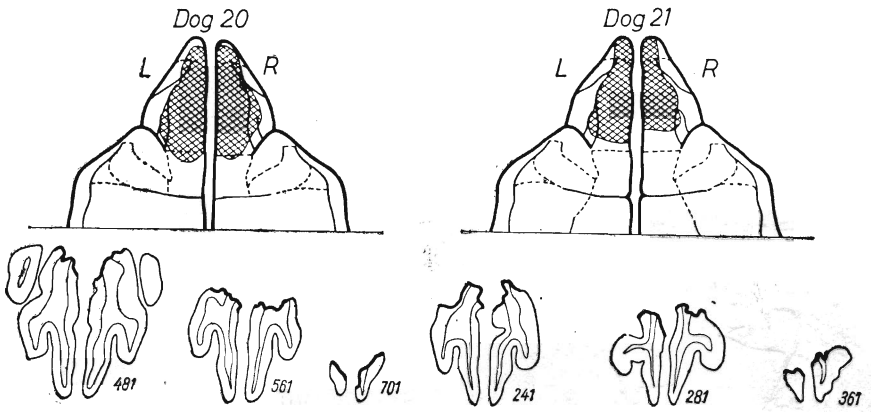

Fig. 9. Reconstruction of the proreal lesions.

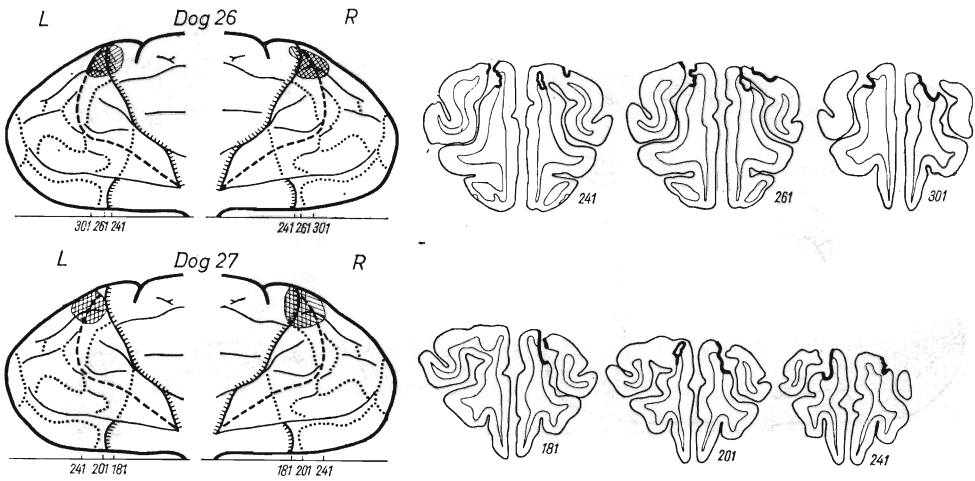

Fig. 10. Reconstruction of the small lesions in the proreal area located in the depth of the presylvian fissure.

and the gyrus pregenualis III and anterior part of XM areas on the medial aspect of the hemisphere. The lesion in dog 25 was located in the orbital area rather in front of the presylvian fissure than in the depth of it. Only the small part situated anteriorly in the depth of presylvian fissure was bilaterally removed. The lesion also included unilaterally part of ORB I' bilaterally part of ORB I'' and ORB II.

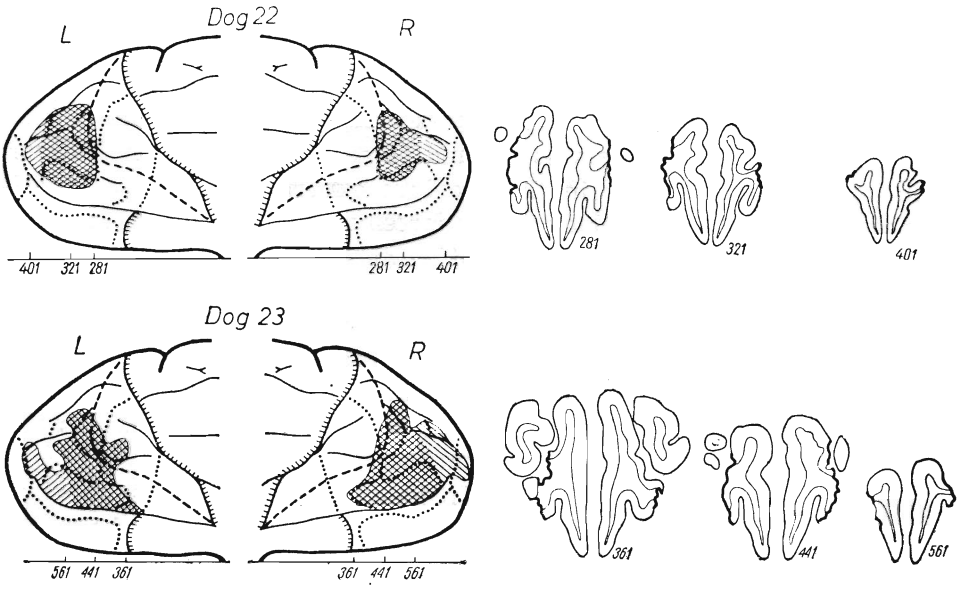

Fig. 11. Reconstruction of the partial orbital lessions.

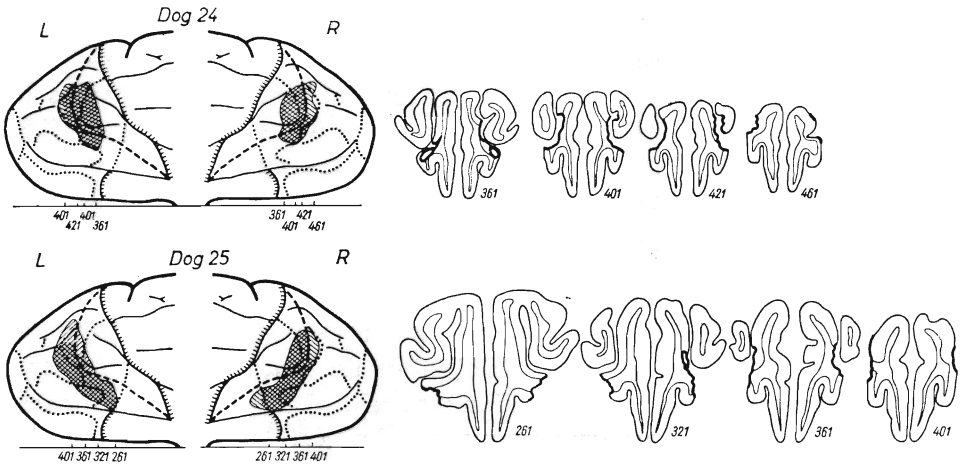

Fig. 12. Reconstruction of the partial orbital lesions extended to the depth of presylvian fissure.

DISCUSSION

Comparison of these results and those obtained by Brutkowski and Dąbrowska (2) shows that there is a crucial difference between the effects of prefrontal lesions on go–no go differentiation test when symmetrical and asymmetrical reinforcement is used. In both types of experiments

the same stimuli were used: tone 1000 cycle/sec (CS_1) positive-excitatory for the instrumental response and tone 700 cycle/sec (CS_2) negative or inhibtory to the same instrumental response. Both tones were given from the same place (one loudspeaker) situated in front of the animal. The different intertrial intervals (15 and 60 sec) were used for different animals both in these and in the previous experiments. The only difference between them was lack of reinforcement to CS_2 in asymmetrical differentiation and the possibility of reward to CS_2 in symmetrical differentiation.

The first difference between two types of experiments is that the length of intertrial intervals is an important agent which may determine the effect of lesions on differentiation with asymmetrical reinforcement, whereas the same parameter does not change the effect of prefrontal lesions upon differentiation with symmetrical reinforcement.

The second difference is that the medial prefrontal lesions impaired transiently asymmetrical differentiation whereas similar lesion had very small or no effect on symmetrical differentiation.

Thirdly, lateral prefrontal lesions impaired very strongly, almost permanently, symmetrical differentiation whereas asymmetrical differentiation was disturbed transiently only when short intertrial intervals were used.

Finally, the errors made after prefrontal lesions were produced only in response to the CS_2 in the asymmetrical differentiation whereas in symmetrical differentiation the errors were made to both stimuli (CS_1 and CS_2); the animal performed the instrumental response to two stimuli or the opposite behavior could be seen when he withdrew the movement to both stimuli.

If we regard the effects of partial prefrontal lesions on these two types of differentiation, it is found that the effect of medial lesions on asymmetrical differentiation test is related to the extent and place of lesion but not to the length of intertrial intervals. But, the effect of lateral partial ablations on this differentiation was related to the extent of lesion and to the length of intertrial intervals. The correlation of lesion size and degree of impairment in the test was observed only in dogs trained with short intervals (2).

On the other hand the effects of partial prefrontal lesions on symmetrical differentiation test were not related to the length of intertrial intervals but to the place of lesion. The strongest and longest impairment was observed in eight dogs (dogs 9-16) with large lateral prefrontal ablations and also in dogs 22 and 23 with small orbital lesions extended to the presylvian fissure. Dog 24, in which the area located under presylvian

fissure was removed, was also severely impaired. But, in this dog the lesion was deep and damaged the white matter under the cortex. The damage of the fibers going to or from the orbital areas was responsible probably for this impairment. Dog 25, which had a larger but less deep lesion than the previous dog, was not impaired in the test. Even deep proreal damage did not affect the retention in this test. Small and moderately deep lesions of the area located in upper part of gyrus compositus led to moderate impairment in the test. But, these damages extended to the lateral precruciate area and probably removal of these areas was responsible for the impairment of these animals. Unfortunately, separate lesions of precruciate areas were not performed, and their effect on the symmetrical differentiation test is not known. These results suggest that the orbital area (ORB I) could be responsible for the severe impairment of go–no go symmetrical differentiation performance.

However, slight impairment was observed also after partial lesions situated on the medial aspect of the hemisphere. Five dogs of these group (dogs 1, 2, 5, 7, 8) were not impaired. Five dogs (dogs 3, 4, 6, 18, 19) were slightly impaired. And, dog 17 was severely impaired. In all dogs the lesions differed largely in their extent and depth. Histological verification of the material has shown that neither of medial cortical prefrontal lesions can be responsible for a small impairment observed in the dogs. The damage of white matter located anteriorly under pregenual gyri also did not affect the test. The retention of this test was impaired only in the case when the damages of white matter were made on the border of pregenual and XM areas and more posteriorly. Dog 17 was severely impaired, he did not reach criterion postoperatively and his performance was quite similar to the performance of dogs with lateral prefrontal lesions. Histological verification of his brain showed that the white matter under anterior part of XM area was cut unilaterally up to the cortical layer of the lateral aspect of the hemisphere. In the other hemisphere the white matter was also damaged but not very deeply.

These results show that when we made the lesion of medial prefrontal cortex, in which we damaged the white matter anteriorly, then the proreal and subproreal fibers can be removed but orbital and paraorbital fibers are spared and the postoperative performance is correct. Now, if the damage of white matter is made more posteriorly in the vicinity of XM areas, orbital and paraorbital fibers can be damaged. In such a case the connections to and from the orbital cortex might be damaged and the test performance was impaired. Unfortunately, there are no direct anatomical data concerning cortical afferent and efferent connections of these

areas in dogs. Therefore, our present explanation remains so far hypothetical only.

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