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IMPAIRMENT OF UTILIZATION OF RESPONSE-PRODUCED CUES AFTER FRONTOPOLAR LESIONS IN RATS

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Abstract. Ablation of the frontal pole was followed by the deterioration of returning behavior; position discrimination in an enclosed T maze was also affected. Both tests required the utilization of response produced cues: In the elevated T maze, in which extra-maze visual cues were available, the lesion had no effect on position discrimination. Introduction of differential visual cues to the enclosed T maze resulted in superior performance of the frontopolar group compared to that of the normal group. However, the visual discrimination experiment did not reveal the superiority of frontopolar rats, which suggests that the frontopolar rats are more attentive to visual stimuli only in situations requiring the use of response produced cues.

In the early period of studies on prefrontal association cortex in a variety of species, the notion was widespread that prefrontal association cortex was absent in lower mammals. The negative reports were discounted in view of finding of thalamo-frontal projection from nucleus medialis dorsalis in rabbits (Rose and Woolsey 1948). This was largely a basis for the conclusion that frontal pole in rats must be a projection field of nucleus medialis dorsalis. Thus, the frontal pole in rats was considered as a homologue of prefrontal cortex in higher forms and this view stimulated the behavioral studies on frontally lesioned rats. The results of a number of experiments were compatible with the findings obtained from other infrahuman species. It was found that frontal lesions in rats produce deficits in delayed alternation (Morgan and Wood 1943, Loucks 1931, Stein et al. 1969) and double alternation (Hunter and Hall 1941); frontal lesions were followed by perseverative errors (Maher 1955, Łukaszewska 1971). Surprisingly, however, ablation of frontal poles did not affect learning of spatial reversal (Thompson 1964, Łukaszewska 1970), which is disturbed by frontal ablations in other species (Mishkin 1964, Warren 1964). The resolution of discrepant results in rats and higher mammals was given by Leonard (1969) who reported, that in rat nucleus medialis dorsalis projects to the medial wall of the hemisphere, anterior and dorsal to genu of the corpus callosum and to the dorsal bank of sulcus rhinalis. After lesion in nucleus medialis dorsalis no degeneration fibers were traced to the convexity of the hemisphere.

Although in previous experiments the lesions often invaded the medial wall of the hemisphere, they certainly did not cover entirely the region delineated by Leonard. This calls for re-examination of the role of frontal cortex in rodent behavior.

The other question not less important concerns the functions of dorsal frontal cortex which does not receive the projection from nucleus medialis dorsalis. Lesions typically described as frontal, differed markedly in size and localization; thus the evaluation to what extent the deficit was produced by damage to medial cortex, and what was contributed by the dorsal part is very difficult. Since in all my experiments, lesions were confined to the dorsal aspect of the hemisphere, it seems that the results obtained may throw some light on the function of the area in question.

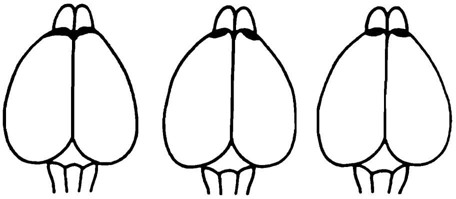

Fig. 1. Representative frontopolar lesions.

Frontopolar lesions. Figure 1 shows typical lesions made in all experiments. Ablations were produced by aspiration of the tiny region which lies anterior to the motor cortex as defined by Settlage et al. (1949). The medial wall of the hemisphere was spared, only its very tip was occasionally damaged.

Returning behavior test. In this test performance of subjects was studied on elevated T maze, which, contrary to a usual T maze, contained two starts located at the ends of the maze arms and only one goal place — at the end of the maze stem (Fig. 2). Both starting platforms were equipped with screens with swinging doors. At the beginning of each experimental session a box with the rat inside was put on one of the platforms. The rat was required to go to the goal, take a reward (it was a small piece of cookie) and return to the box where he was allowed to eat. The subject approaching the incorrect platform on his way back found the screen door locked, but was permitted to correct himself. After finishing one food portion the rat immediately went for the other one, starting the next trial. Thus the intertrial intervals were controlled by the behavior of the subjects, on average 30–40 sec. It should be noticed that this test was a variation of delayed response test. From start to the goal the animal was probably guided visually by the sight of the cup, or he learned not to approach the opposite maze arm but to take a turn to the maze stem. However, when he returned, he did not see the box. At the moment of decision the animal must remember from which platform he started. In other words, at the choice point he responded not to actual stimuli but to the traces of stimuli acting several seconds earlier. It was found previously (Łukaszewska 1963) that the predelay stimulus determining the correct response is elicited by a turn taken on the way to food. Thus, if going for food the rat performed, e.g., a left turn, he must perform the right turn when he returned. Time which elapsed between the first and the second turn constituted the delay period. With the length of the maze stem used which was 40 cm the delay varied from 3 to 5 sec depending how fast the subject ran.

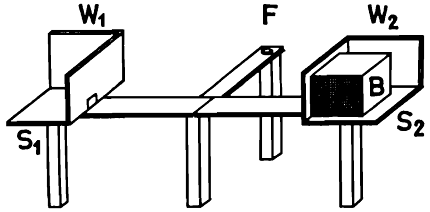

Fig. 2. Apparatus used in returning behavior test. S_1, S_2, starting platforms; B, box; W_1, W_2, wooden screens; F, cup with food.

Using this procedure the performance of normal and frontopolar rats was tested during 10 successive days. Three daily trials were applied in which the subject started from the same platform; the position of start was changed from day to day in alternative sequence. Figure 3 shows the comparison of performance of frontopolar and normal rats in terms of percentage of correct responses scored by the whole group during the testing period. The percentage of correct responses is shown separately for each daily trial. Normal group performance was very efficient; in Trial I above 90% of correct responses were observed and this percentage increased up to the level of 100% in further trials. Frontopolar lesions resulted in moderate but statistically significant ($p < 0.05$, Mann-Whitney U test, two tailed) decrease in performance in all three trials, with the most pronounced difference in Trial I. Figure 4 presents the pre- and post-operative performance in frontopolar and control operated

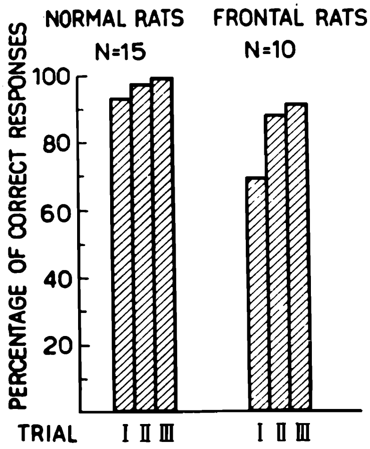

Fig. 3. Performance of normal and frontopolar rats in returning behavior test. *I–III*, successive trials of every experimental session. Each bar represents the percentage of correct responses of all *S*s during 10 days' test.

rats which received lesions of the same size in occipital cortex. Following the frontal operation the performance of subjects clearly deteriorated in Trial I, while that of occipitally lesioned rats remained on the same level. In this experiment, in Trials II and III frontopolar subject performed as well as before operation. Thus, it seems that frontopolar lesions

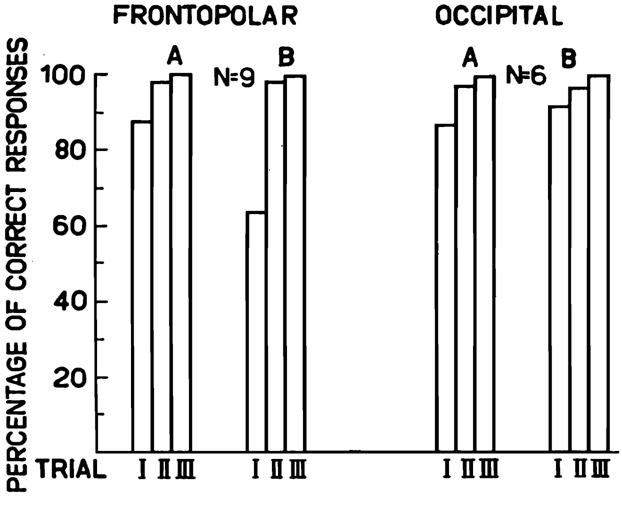

Fig. 4. Pre-operative and post-operative performance of frontopolar and occipital rats in returning behavior test. *A*, before operation, *B*, after operation. Denotations as in Fig. 3.

do not affect the performance in trials in which subjects simply repeat the return run from the preceding trial.

Viewing the returning behavior as a delayed response test, as an explanation of the deterioration in performance of frontopolar rats one of the current interpretations of similar deficit in higher mammals was accepted (Łukaszewska 1968). However, it should be stressed that in the returning behavior the predelay cue is generated by the animal's turn on the way to food, thus, it is also conceivable that frontopolar lesions impair utilization of response-produced cues.

Position discrimination in enclosed and elevated T maze. In order to collect further samples of behavior, presumably requiring the use of response-produced cues, it was attempted to compare the performance of frontopolar and normal rats on position discrimination in the enclosed T maze, in which only response-produced feedback was available, and on elevated T maze, where the subjects might be guided by visual extramaze cues as well. The apparatus used in the experiment was so constructed that the enclosed T maze could be easily converted into the elevated one and vice versa, depending on which group was actually run. This was done by putting the platforms which fitted the top on the enclosed maze, or by removing them. In both mazes two goal boxes were placed at the ends of the maze arms, 75 cm from the choice point. The subjects were run for food for 12 trials a day with intertrial intervals of 4–6 min. One day before the start of the experiment each subject was given a single preference trial in which both goal boxes contained reward. For half of the subjects in each group the preferred side was positive, for the other half — the non-preferred one. The position of reward was reversed when the subject met a criterion of 12 successive correct responses. Four reversals were applied. As may be seen in Fig. 5, in initial learning in the enclosed T maze frontopolar group showed a higher number of errors than the normal one. Analysis of variance showed that the difference is highly statistically significant ($p < 0.01$). In Reversal 1 and 2 the difference in performance although still signif-

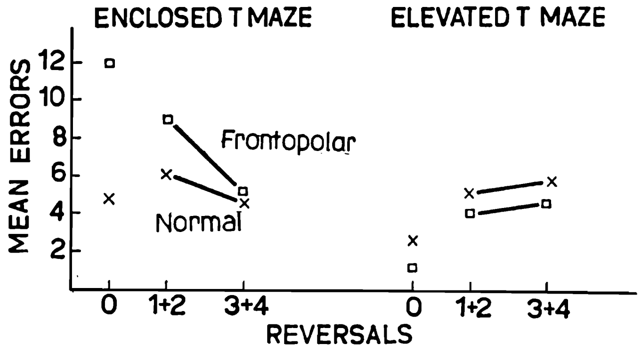

Fig. 5. Comparison of performance of normal and frontopolar rats in enclosed and elevated T maze. In both groups the number of subjects = 10.

icant diminished and finally disappeared in Reversal 3 and 4. In contrast, in the elevated T maze frontopolar rats did not differ from normal rats either in the initial learning or in successive reversals. As a matter of fact, frontopolar group showed even somewhat lower error scores than the normal one, although the difference did not reach the accepted level of significance. Comparison of performance of normal rats in two different mazes indicated no significant difference, while frontopolar rats performed much better on elevated T maze than in the enclosed one ($p < 0.01$). Apparently, on elevated T maze, frontopolar rats were guided by visual extra-maze cues; the absence of differential visual cues in the enclosed maze made the task much harder. Normal rats either used response-produced kinesthetic stimuli as discriminative cues in both mazes, or they could use the response-produced cues and extra-maze visual cues equally efficiently. The finding that the difference between the performance of frontopolar and normal rats in enclosed T maze tended to disappear in the course of successive reversals indicate that the deficit was related rather to attention to response-produced cues than to entire inability of their utilization.

The effect of intra-maze visual cues in the enclosed T maze on position discrimination. Since the performance of frontopolar rats did not differ from that of normal rats when extra-maze visual cues were present, this experiment was designed to test whether the visual differentiation of alleys in enclosed T maze would have a similar effect. The alleys of the same apparatus as in the preceding experiment were equipped on their entire length with interchangeable metal inserts. The walls of one insert and the door of the corresponding goal box were painted with alternating white and black horizontal stripes, while the other insert had the walls painted with vertical stripes and so was painted the door of the other goal box. For all animals the positive side was the not preferred one in single preference trial which preceded the start of experiment. For half of the subjects the positive alley was provided with horizontal stripes for the other half — with vertical stripes. Ten trials were given per day with 4–6 min of interial intervals until the criterion of 18 out of 20 trials on two consecutive days was reached. It was found that under conditions of visual differentiation of the alleys, frontopolar group performed better than the normal one (Table I). The difference were significant (Mann–Whitney U test, two tailed).

After reaching the criterion each subject was given at the same experimental session a single trial in which position of visual cues was reversed. This trial constituted the test for dominance of cues (visual vs. spatial). Surprisingly, when faced with the situation in which visual and spatial cues gave contradictory information the majority of frontopolar as well as normal animals turned to the side to which they had been trained. Only five rats from each group responded on the basis of visual cues, but almost all rats showed some hesitation at the choice point.

TABLE I

Mean scores for learning in enclosed T maze with differential visual cues

Group	N	Trials to criterion	Errors
Normal	20	20.0	7.4
Frontopolar	17	11.7*	4.3**

* $p < 0.05$.
** $p < 0.02$.

This experiment indicates that although frontal rats performed better in the just described two cue situation, they apparently did not pay attention to visual cues alone. The way in which intra-maze visual cues facilitated position discrimination is not clear. One may suppose that they formed jointly with spatial cues the compound visuo-positional stimuli, which were more discriminative for frontopolar than for normal rats, or, the role of intra-maze visual cues consisted only of switching the attention of subjects to spatial cues. Certainly more experimental data are needed to elucidate this problem.

Visual discrimination masked by position reversals. In some situations intra-maze visual cues may function independently of positional cues. This was found in one of the series of experiments on visual performance in frontopolar and normal rats (Łukaszewska 1970). One group of normal rats and one of frontopolar rats were trained on position discrimination and several successive reversals on the elevated T maze, with arms 50 cm long, painted gray. The other two groups of normal and operated rats were presented with the same problem in the maze which was identical as the previous one, except that one arm was painted white and the other — black; the maze stem was grey. All subjects were trained for 12 trials a day until criterion of 12 successive correct responses was achieved in one experimental session. In white-black maze, after a subject met criterion, the position of reward was transferred to the other maze arm together with the color.

In this way, for each subject the same visual cue was consistently rewarded throughout the series of spatial reversals. Thus, the subject could solve the problem in two different ways: as a visual discrimination if he ignored positional cues, or as successive reversals of position if he ignored intra-maze visual cues. In the latter instance the reversal learning curve should not differ from the respective curve obtained in the previous group on position reversals with no intra-maze visual cues. As may be seen in Fig. 6, the performance of frontopolar rats in two different mazes was the same in initial learning and in Reversal 1. Starting from Reversal 2 the curves deviate and the difference between them is statistically significant ($p < 0.05$, Student's t test). It means that already in Reversal 2 frontopolar rats begin to pay attention to intra-maze visual cues. In normal rats (Fig. 6) the difference in performance on two different mazes reached the accepted level of significance in Reversal 5, indicating that normal rats switched to visual cues considerably later.

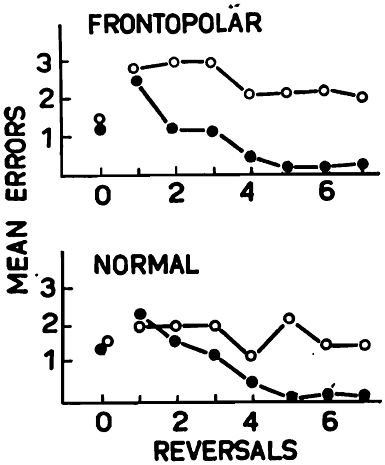

Fig. 6. Comparison of position reversal learning with no intra-maze visual cues (open circles) and position reversal learning with intra-maze visual cue consistently associated with reward (filled circles). In each group the number of subjects = 6.

Visual discrimination. In spite of the fact that frontopolar rats can use the visual cues very efficiently in position discrimination problems, their performance in visual discrimination proved to be not superior to that of normal rats. Three experiments were performed using different apparatus and different visual stimuli: (i) elevated T maze with white-black arms, (ii) modified Lashley apparatus with white and black stimulus cards, and (iii) Thompson box with stimulus cards painted with horizontal and vertical white-black stripes. In all three experiments no differences were found between the normal and frontopolar groups, either in initial learning or in reversal learning (Fig. 7). Obviously frontopolar rats pay more attention to visual stimuli only in situations requiring the utilization of response-produced cues. Thus the finding of Jeeves (1967) that frontopolar rats showed superior performance to normal rats in initial learning of visual discrimination and in several successive reversals was not replicated. However, it should be noticed that in Jeeves' study the lesions were placed not exactly in frontopolar region, but somewhat more posterior.

Previous data supporting the hypothesis. The notion that frontopolar lesions impair discrimination of response-produced cues receives some experimental support from previous data on rats with similar damage.

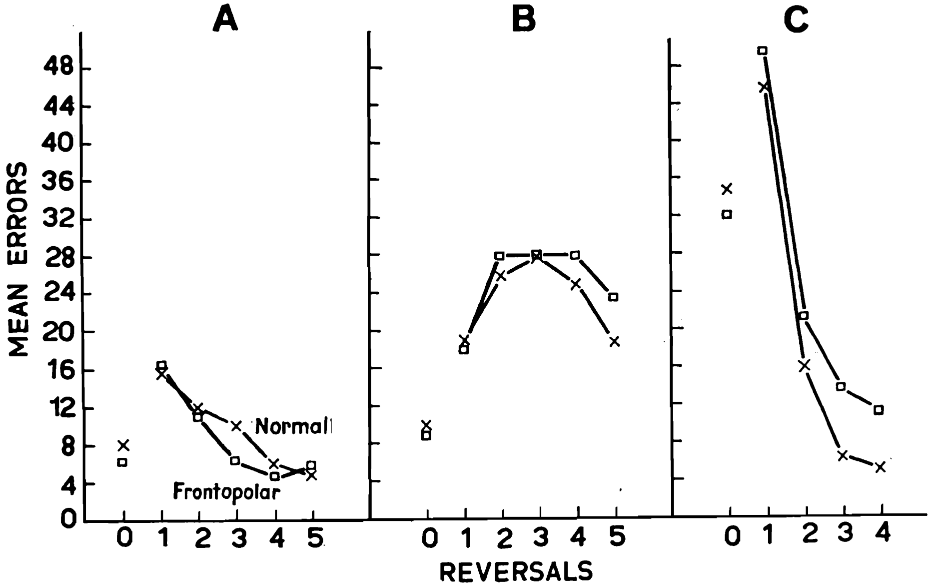

Fig. 7. Visual discrimination learning and successive reversals in normal and frontopolar rats. *A*, elevated T maze; *B*, modified Lashley stand; *C*, Thompson box. In *A* the number of subjects in each group is 6, in *B*, 12 and in *C*, 11.

Gross, Chorover and Cohen (1965) showed that frontal rats were deficient in the two bar alternation task. The absence of any intra-delay made it difficult, according to the authors, to characterize the deficit as one of recent memory; also the deficit could not be ascribed to inhibition or response perseveration. In the authors' opinion, interpretation of the deficit as one in response chaining might be possible. This interpretation certainly sounds similar to impairment in utilization of response-produced cues.

Even more informative experiment in this respect was made by Dąbrowska (1964). In her experiment rats learned successively different routes in four unit apparatus. In normal rats, the number of trials needed to learn successive problems decreased and finally the animals were able to master the problem in two or three trials, which suggested that normal rats gradually acquired the capacity to integrate the separate motor responses into single zig-zag like motor-acts. In contrast, rats with frontopolar lesions showed no evidence of response chaining.

Another example of impairment of utilization of response-produced cues may be found in the experiment of Stellar, Morgan and Yarosh (1942). In this experiment rats were required to run along the elevated maze for a fixed distance and then to turn left for food. Exteroceptive stimuli could provide no guidance. It was found that lesions in the frontal pole interferred with retention of the habit. The authors regarded this task as symbolically mediated but, it also may be considered as distance discrimination based on kinesthetic cues produced by animal locomotion.

In view of the finding of Leonard (1969) that nucleus medials dorsalis does not project to dorsal convexity in rats, this region cannot be any longer homologized with frontal association cortex of other species. There is some tendency to consider the frontopolar region in the rat as a premotor cortex (Divac 1971). The paucity of studies on premotor cortex prevents the valid comparison of behavioral deficit in rats and higher mammals, but certainly there are some similarities. Yamaguchi, Warren and Hara (1963) observed after removal of the premotor cortex in cats the deficit in post-operative retention of single alternation, which is possibly based on discrimination of cues produced by the animal's own performance. On the other hand, the deficit in utilization of response produced cues was observed by Wagman (1968) in frontal cats. However, although the lesions were followed by degeneration in nucleus medialis dorsalis, some part of premotor cortex was also damaged. It should be mentioned that using the same experimental procedure as Wagman (1968), Ellen and Kelnhofer (1971) replicated her results on septal rats. The septal area is known to be related to prefrontal cortex. In view of these facts it seems that frontopolar region in the rat constitutes a transitional area between prefrontal and premotor cortex. The functional boundary between the prefrontal and premotor cortex is much less defined in the cat than in the monkey and this may be even more applicable to the rat cortex.

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