THE EFFECT OF ANTERIOR THALAMIC NUCLEI LESIONS UPON CONDITIONED AVOIDANCE RESPONSES IN RAT

Fritz KLINGBERG and Herta KLINGBERG

Department of Neurophysiology, Paul-Flechsig-Institute for Brain Research, Karl-Marx-University Härterlstrasse 16/18, 701 Leipzig, GDR

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Abstract. Three groups each of 7 hooded rats had bilateral symmetric lesions of the n. anterior ventralis the n. anterior medialis and n. anterior dorsalis and were compared to two groups of 7 nonoperated control rats. After the lesions no changes in spontaneous behavior, sensory or motor functions, body weight, reaction type and thresholds to painful footshocks were observed. The postoperative acquisition of a one-way conditioned avoidance response in a simple runway task was significantly retarded in ventral and medial rats and impossible in dorsal rats. While escape reactions were not impaired, lesioned rats had troubles passing the start door early after the onset of the conditioned stimulus. During alternation training of avoidance responses, the ventral and the medial rats preferred one side of the Y-maze. When they learned to run to the illuminated exit as a high-probability stimulus after several sessions, the entire stereotype became more unstable and the percentage of avoidance responses decreased. None of the lesioned rats escaped shock in a pole-climbing test, which was characterized by very low probability of correct response in the first session. These anterior thalamic nuclei are part of the Papez circuit which may be the main substrate for learning and retrieval of problems with low probability.

INTRODUCTION

One of the syndromes in human memory pathology is the Korsakoff amnesic syndrome (1, 41). Korsakoff patients find it difficult or impossi-
ble to form any permanent new memories or even to retrieve old memories. Investigators of this syndrome came to the conclusion that probably the hippocampus plays a key role in memory formation. Poschel (25) postulated that the Korsakoff amnesic syndrome is likely to result from bilateral damage to any part of the brain circuit of Papez (24, 42), in which anterior thalamic nuclei are enclosed.

Since the functional role of anterior thalamic nuclei has been rarely investigated, we analyzed avoidance learning after lesions of these nuclei in an experimental procedure characterized by increasing difficult tests. The main input to the nuclei anterior medialis (AM), anterior ventralis (AV), and the anterior dorsalis (AD) comes through mammillothalamic tract (MTT) (3, 43). Their main output projects to the cingulum which is richly interconnected with several regions of the brain and from which a strong feedback pathway returns to the anterior thalamic nuclei (4, 5, 13, 42).

METHOD

Groups of 6 mo old male hooded rats of the LONG-EVANS strain were trained to avoid footshocks in tests with increasing difficulties. Their body weight ranged from 280-350 g. The rats were housed in groups of 7 and had free access to water and standard food pellets. Each experimental group consisted of 7 rats.

The apparatuses used in the experiment were a Y-maze and a box for a jumping test. The Y-maze consisted of three 50 cm long, 12 cm broad and 12 cm high branches with a metallic floor grid for electrical stimulation from a square wave generator. The branches were arranged symmetrically forming angles of 120 degrees. The start box (15 X 12 X 12 cm) and the two goal boxes (25 X 15 X 15 cm) were separated by transparent one-way doors. These initiated response stop of electric stop-watches when they were opened. During the stimulus interval, the start box exit was closed until the onset of the conditioned stimulus (CS). The CS was a 1 kHz tone of 5 s duration with a constant intensity of about 60 dB from a small loudspeaker on the lid of the start box. The unconditioned stimulus (UCS) was electric footshock beginning 2 s after the offset of the CS. The parameters of the UCS were 90 V, 30 imp./s, 15 ms/imp. with a maximal duration of 10 s. The correct exit with goal door unlocked was illuminated by a small 10 W lamp. No other cues were available for the rats. One of the goal branches could be closed at its begin for testing in a simple runway experiment.

The jumping test (pole-climbing test) was performed in a 30 cm broad, 35 cm long and 45 cm high test box. A wooden rod (3 cm diameter) was hanging in the middle of the cage, with its end suspended 5 cm above
the grid floor that conducted the UCS (50 V/50 Hz alternating current). The CS was a 1.5 kHz tone from a loudspeaker on the lid of the box preceding the UCS by 3.5 s. Its intensity of about 60 dB remained constant throughout all experimental sessions. Two electric stop-watches were used to measure the reaction times and the durations on the rod. They began and stopped with the action of the CS and by contacts at the upper end of the rod. The tests were performed under conditions of weak background illumination and constant room temperature (22°C). The sequence of tests with increasing difficulty were conducted daily and was as follows:

1. The runway test was administered in the Y-maze with the right of the 50 cm long branches closed for 10 trials per session.

2. The alternation test (2:2 schedule) was given also in the Y-maze with the same CS–UCS parameters for 20 trials per session. The correct exit (unlocked goal door) was illuminated.

3. The jumping test (pole-climbing test) required subjects to avoid the shock (50 V/50 Hz alternating current) by jumping (climbing) on a hanging rod.

All animals received the opportunity to explore the apparatus for habituation before the sessions. Stimulus parameters and the other conditions remained constant throughout all testing series. Trial intervals were varied randomly from 30 s to 3 min to eliminate temporal conditioning. Subjects' first contact with any apparatus was 10 days after lesions.

Small bilateral symmetric lesions were administered stereotaxically by constant anodal currents (1 mA, 15 s) in three groups: the anteromedial (AM), the anteroventral (AV) and the anterodorsal (AD) thalamic nuclei. The stereotaxic coordinates for the tip of the anode were, according to the atlas of Fifková and Maršala (1967): AM: OP 1.2, lat. 1.0, vertic. 5.8; AV: AP 1.2, lat. 1.5, vertic. 5.0; AD: AP 1.5, lat. 1.0, vertic. 4.3. Two nonoperated groups were used as controls, one together with AM and AV rats and the other with AD rats, which were examined several months later. The extension of the lesions was checked histologically using Nissl stains. Group differences in correct conditioned avoidance responses (CAR), reaction times (RT, latency from onset of CS to passing the start door), duration of runs (R, time between passing the start and the goal door) and errors were evaluated with non-parametric Mann-Whitney U tests.

RESULTS

AM and AV lesions. Lesioned rats showed no evident differences in their spontaneous behavior, body weight, reaction type and thresholds
to foot-shocks when compared with control rats. Their reflex status and locomotive patterns remained unchanged after the lesions.

Figure 1 shows localizations and sizes of the lesions in the AM from 6 rats; one rat had incorrect lesions and was eliminated from the experiment. The lesions in the AV are shown in Fig. 2. From the very begin-

![Fig. 1. Schematical drawings of localizations and sizes of the AM lesions from six rats in the plane of their maximal extent.](image)

ning of the experiment, all lesioned rats evidently had more trouble adapting to changing environmental conditions. This was most obvious during the first trials in the runway test. The lesioned animals did not easily find the way to pass the start door while they ran forward to the exit door, compared to control rats. The acquisition of the relationship between the CS and leaving the start box was significantly retarded. This finding was expressed in significantly prolonged RTs \( (P<0.01, \text{ Fig. 3}) \). The AV-and the AM-rats needed significantly more trials to reach criterion and thus received more foot-shocks than did the controls. Compared with the control groups, they reached the CAR criterion of 5 successive correct responses or more than 70% CARs in two subsequent sessions 3 sessions later (Fig. 3). There was no difference in the duration of runs (running speed about 0.4 m/s).

When the left side branch of the Y-maze was closed and the right branch was opened in the runway test of the 7th day, we did not observe
essential changes and differences (Fig. 3, arrow "a"). However, alternation training with left and right branches open, beginning on the 8th day, seemed to be difficult for both lesioned and control rats. When the rats chose the closed branch, they had to turn and to run twice the distance to the open exit, which resulted in an increase of the running duration and the number of foot-shocks. Consequently, CARs decreased (Fig. 3, arrow "b"). The group mean of errors was hardly different: lesioned rats chose the false branch on 50% and controls on 40% of the trials during the first two sessions (Fig. 4). From these data, it was apparent that the running speed was unchanged until the shock onset. The lesioned rats hesitated when confronted with the closed exit. Consequently, their running duration increased more than that of control rats. Their RTs, on the other hand, remained unchanged. The control rats hesitated in the start box, so that their RTs increased significantly (Fig. 3).

All rats preferred the left side of the maze at the beginning of al-
Fig. 3. Mean values of conditioned avoidance responses (CARs), running duration (Rs) and reaction times (RTs) in the Y-maze after bilateral lesions of AV nucleus (solid line with opened circles, seven rats); AM nucleus (dashed line with opened circles, six rats) and from control group (solid line with filled circles, seven rats); 1st–6th days: running to the left side (10 trials per session); 7th day: running to the right side (10 trials); 8th–14th days: 2:2-alternation (20 trials per session). Interindividual standard deviations are indicated on days with significant group differences (P < 0.01).

alternation training. While control rats tried both sides at some point during the first session and their errors became equalized, the lesioned rats preferred the left side throughout several sessions (Fig. 4). For this reason, errors were stereotypically stable at 50%. The inhibition of incorrect

Fig. 4. Mean values of incorrect runs (errors) on subsequent days of alternation training corresponding to Fig. 3. Solid line with filled circles, errors total; solid line with opened circles, incorrect runs to the preferred (left) side; dashed line with opened circles, incorrect runs to the not preferred (right) side.
responses developed very slowly after the lesions, more slowly after AV lesions than after AM lesions. With the strengthening of this inhibition, the activation for starting became increasingly weaker and the RTs increased (Fig. 3). The same observation was found in the control rats by the first alternation session. With increasing memory storage, this pattern was soon overcome in controls and RTs decreased again. Such was not the case in the lesioned rats, in which the memory storage of the complex task was not stabilized and the percentage of CARs decreased continuously. Their escape performance remained unchanged during subsequent sessions. Finally, we observed that the correct performance of CARs decreased even during the improvement of light-dark discrimination (reduced errors).

In the jumping test the lesioned rats made several types of jumps during foot-shocks and also ran against the rod hanging in the middle of the cage, but they did not acquire the escape behavior. The low proba-

![Fig. 5. Mean values of conditioned avoidance responses (CARs), running duration (Rs) and reaction times (RTs) in the Y-maze (only left branch open) after bilateral lesions of the AD nucleus (solid line with opened circles, five rats) and from a control group (solid line with filled circles, six rats). s, time in seconds.](image-url)
bility of shaping adequate behavior in the jumping test was easily acquired by the control rats that reached the criterion in the fourth session.

**AD lesions.** Lesions of the AD were only obtained with damage to other structures. Small parts of the commissura fornicis, the anterior pole of the hippocampus and a larger part of stria medullaris were involved in the lesions. Figure 5 shows the mean values of CARs, RTs and running durations (Rs) from the runway test, after AD lesions in 5 rats with partial destruction of the stria medullaris, which are compared with the results of the second control group. While their escape reactions were not impaired and the duration of runs was even significantly shorter than in the controls ($P < 0.01$), the lesioned rats did not reach stable CARs (Fig. 5). They never attained more than two subsequent CARs and thereafter waited until the foot-shock onset during the next trial. For this reason their CAR mean values oscillated between 30% and 60% and their RT correspondingly between 6 and 4 s. We regularly measured two groups of RTs: above 7 s, when foot-shocks were not avoided and below 3 s, when they were avoided. All sessions began with nonavoidance. Further training sessions with increased difficulties were ineffective. Also in this group no rat found the possibility to escape in the jumping test.

**DISCUSSION**

All rats with AM-, AV- or AD-lesions exhibited, to varying extents behavioral deficits in active avoidance learning, depending on the difficulty of the task. The unchanged pain reaction thresholds, running durations and escape patterns indicated that the deficits were not due either to disturbances of motor performance or to changes in the pain motivation. Also fear motivation seems to be unchanged. The lesioned rats everytime displayed emotional activation when put into the start box, and they tried to get out. Since the box was closed until the onset of the CS, the rats learned to leave the box only soon after the CS onset. Accordingly, we have evidence that the lesioned rats preserved the ability to avoid punishing stimulation.

The lesioned rats behaved differently from the control rats in situations with changing environmental conditions. This behavioral deficit increased with the decreasing probability of correct responses. They easily acquired responses on the basis of high-probability events. In changing situations, they reacted stereotypely and needed more trials and more reinforcements than controls to change from the former stereotype. Thus, during alternation training lesioned rats always preferred the left side of the Y-maze. They always ran the same way, e.g., first to the left and when the left exit was closed, then to the right side. Some success of this strategy may have led to a decrease of fear. The acquisition of a ste-
reotype with variable parameters seems to be impossible after anterior thalamic lesions. This observation was more evident the more variable was the stereotype. When the high-probability connection between illumination and open exit became dominant against the lower probability of left versus right, the errors of lesioned rats decreased. Then, they seem to “forget” leaving the start box in good time. We suggest that this finding is the consequence of changing the stereotype, during which less stable elements become more strongly inhibited. In agreement with Pavlov’s ideas, the dark exit as a no-go signal becomes the conditioned inhibitor. The strengthening of this behavioral inhibition consequently influenced RTs and Rs which increased despite the decreasing errors made by AV-and AM-rats.

Behavioral investigations after anterior thalamic lesions are rare. We cannot compare our results, unfortunately, with those of Thompson and co-workers (26, 30, 32, 33, 35, 36) who investigated behavioral deficits of rats after large lesions in the anterior thalamic complex with varying amounts of damage to the AD, AM, AV, the medioventral, parataenial nuclei and stria medullaris. They found that the anterior thalamic complex is critical for retention of skilled movements, e.g., latch box performance (36), for a vestibulo-kinesthetic discrimination habit, a maze habit, but not for brightness or pattern discrimination habit (34). These investigators found similar disturbances when they damaged other regions like the dorsomedial, ventromedial, ventrolateral, ventrobasal and parafascicular nuclei of the thalamus, each of which is known to have connections with frontal, parietal and/or anterior cingulate areas.

In contrast, we found that after bilateral symmetric lesions of the n. dorsomedialis thalami, rats never tried to avoid foot-shocks but correctly performed escape reactions (15). They showed no signs of emotional activation when put into the apparatus. Further, we saw quite different disturbances and deficits after lesions of the ventromedial (7), the ventrolateral (12) or the parafascicular nuclei of the thalamus (9). We suggest that the more severe disturbances after AD lesions in our experiment may result from the partial destruction of the stria medullaris, which is essential to avoidance acquisition (28).

The most important functional connection of anterior thalamic nuclei is their integration into the Papez circuit. There is evidence that the interruption of this circuit anywhere causes similar functional deficits. Krieckhaus (16) found that complete or partial destructions of the mammillothalamic tract (MTT) affected the retention of a two-way active avoidance but less, a one-way active avoidance task. It was suggested that the deficit produced by MTT lesions was unrelated to the difficulty of the task, but seemed to be related to the extent of the animal’s underta-
king the required response (18). On the other hand, we found increasing deficiencies with increasing difficulties of the task which are the consequence of the decreasing probability of correct responses and results. In the jumping test the probability to find the escape possibility in the first session was extremely low, and it was never learned by any of the AV-, AM- or AD-rats.

It may be debated whether the learning or memory deficit may be caused by an impairment of the ability to perform a spatial discrimination in a T-maze after MTT lesions (19, 31, 38). Behavioral deficiencies after lesions of the Papez circuit can be interpreted as the disturbance of the acquisition of behavioral strategies in changing environmental conditions and of the permanent memory for low probability events which is disturbed after such lesions. This possibility is supported by results from several lesion studies concerning the mammillary bodies (17, 27, 29, 37, 38), the hippocampus (8, 11, 13, 14, 21, 23, 25, 40, 42), the fornix (8, 20, 22), and the cingulum (2, 6, 10, 39). Vinogradova (42) postulated the hypothesis that the Papez circuit contains a sequence of integrators with increasing critical thresholds for repetitions of informations in the context of effective adaptation. The excitation of neurons increases more slowly with repetition of the stimuli the more distant the neurons are situated from the CA1 pyramidal cell layer of the hippocampus, which is further dependent on the informational significance of the stimuli. The acquisition of a conditioned discharge of neurons in the circuit requires more trials when the probability of stimulation and/or experimental arrangement decreases or is low. Vinogradova's hypothesis can serve as a rather good neurophysiological model for the interpretation of such behavioral observations as we have described here. There is no reason to restrict the function of the Papez circuit to spatial discrimination and to place learning.

In our experiment the lesions were small and the deficiencies occurred after partial interruption of the Papez circuit. In these cases the animals attained a certain degree of low-probability learning on the basis of the remaining neuronal circuits. The aggravation of low-probability learning after partial destruction of the Papez circuit has several secondary consequences which may be different when using different experimental paradigms.

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