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ANIMAL AND HUMAN PHYSIOLOGY

The Effect of a Caudal Hippocampus Lesion on Learning in a Morris Water Maze in Bank Voles (*Clethrionomys glareolus*)

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Abstract—The involvement of the caudal hippocampus in spatial learning is presently uncertain, compared to the well established role of the dorsal region. Therefore voles (*Clethrionomys glareolus*) with large (about 1/3 of the whole hippocampus) caudal cytotoxic lesions were tested in the Morris water maze. A version of the test intended to measure long term spatial memory was used. The lesion inhibited the learning process, as well as reducing the accuracy of platform location memory at early stages of training. The data obtained indicate the involvement of this area in control of spatial learning in rodents.

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The hippocampus is a part of the forebrain that has attracted the attention of researchers for a long time. Investigation of the principles of how this structure functions is of both fundamental and practical interest, since hippocampal dysfunction occurs in Alzheimer's disease and in temporal lobe epilepsy. Although the functions of the hippocampus and its different regions in animals and humans are still a subject of debate, the role of hippocampus in memory and spatial learning is unquestionable (Vinogradova, 1975; O'Keefe and Nadel, 1978; Morris et al., 1982; Bast, 2007; Moser et al., 2008). In addition, the hippocampus, as a part of the limbic system is involved in control of anxious behavior (Bannerman et al., 2004; Royer et al., 2010).

The rodent hippocampus includes a region adjacent to the septum, occupying the dorsal rostral area and a caudal temporal area located more ventrally. There is much evidence of hippocampal functional heterogeneity along the rostrocaudal axis. One of the most studied parts of the hippocampus is the rostral area, while studies of its caudal part are fewer and their ambiguous results are the subject of debate (Bannerman et al., 2004; Yartsev, 2010).

A number of researchers (Moser et al., 1993, 1998; Kjelstrup et al., 2002; Bannerman et al., 2004; Czerniawski et al., 2009; Fanselow and Dong, 2010; McHugh et al., 2011) have suggested that spatial learning is performed mostly by the rostral part of the hippocampus. A lesion of the caudal part does not affect performance of spatial tasks in the Morris water maze and radial maze (Moser et al., 1993; Bannerman et al., 2004). This suggestion is concordant with anatomical details: the visual information essential for successful spatial learning passes through the entorhinal cortex and is mainly processed in the rostral hippocampus, while.the caudal part receives information concerning regulation of motivation, emotion, and anxious behavior from the hypothalamus and amygdala (Bast, 2007; Kerr et al., 2007).

At the same time, however there are data indicating the involvement of the caudal hippocampus in the control of spatial learning. It has been shown that a lesion of this region impairs learning in some versions of the Morris water maze (de Hoz et al., 2003; Ferbinteanu et al., 2003; Loureiro et al., 2012). Activation of the caudal part of the hippocampus was observed in rats, mice, and voles in maze learning (Vann et al., 2000; Kuptsov et al., 2005, 2012). As in the rostral part, in this area place cells are found which show a high rate of firing whenever an animal is in a specific location, although the spatial specificity of these neurons is less pronounced (Jung et al., 1994; Poucet et al., 1994; Kjelstrup et al., 2008).

Most of the studies devoted to investigation of hippocampal functions have been performed on rats. We chose for this experiment bank voles *Clethrionomys (Myodes) glareolus* that can be used in the laboratory (Vandebroek et al., 1999) and successfully trained in the Morris water maze (Pleskacheva et al., 2000).

The present study aimed to estimate the involvement of the caudal hippocampus in the processes of spatial learning, using a cytotoxic lesion technique with bank voles in the Morris water maze.

METHODS

The experiment was conducted on 25 young (3–6 months old) male voles *C. glareolus*, caught in live traps at Zvenigorod Biological Station of Moscow State University. The animals were fed ad libitum with a standard mash combined with fresh herbs and vegetables. Voles were randomly divided into experimental ($N = 11$) and control ($N = 14$) groups. The selective hippocampus lesion technique, developed for laboratory mice (Deacon et al., 2002), was adapted by the author for bank voles. Voles from the experimental group underwent a bilateral cytotoxic partial lesion of the hippocampus.

The animals were anesthetized with Nembutal sodium (40 mg/kg), administered intraperitoneally. Additionally, muscle relaxant and tranquilizer chlordiazepoxide in a dose of 20–30 mg/kg were injected. The lesion was made using a stereotaxic instrument (David Kopf Instruments, CA, US) equipped with a microsyringe and microdrive. Single injections of NMDA (N-methyl-D-aspartate) in a concentration of 10 mg/mL were made on each side of the caudal hippocampus (rostrocaudal +0.16 cm from bregma, lateral ±0.3 cm from the midline, dorsoventral –0.4 cm from the surface of the skull at lambda; the injection volume was 0.4 μL). The control animals were subjected to sham operations that included anesthesia, opening the scalp, and stereotaxic introduction of a needle into the brain.

After behavioral experiments, the animals, under deep anesthesia, were subjected to transcardial perfusion with 4% paraformaldehyde. Brain slices of 20 μm thickness were cut on a freezing microtome and Nissl stained. Then the lesion volume and the nature of the damage at different rostrocaudal levels, which was determined using the atlas of the bank vole brain (Vandebroek et al., 1999), were assessed.

The behavioral experiments were conducted not earlier than two weeks after the end of the operations. The voles were tested in the Morris water maze (Morris, 1984). The diameter of the water pool was 130 cm; the height of the walls 30 cm. The pool was filled with water up to 20 cm in height. The temperature of the water was maintained at 23–25°C. The water maze was located in a room with posters and furniture around the walls.

The trajectories of animal movements were recorded using an automated videotracking system consisting of a Sony video camera (Japan) located 2 m above the arena and a computer equipped with an extra Picolo frame grabber (Netherlands). The program EthoVision 3.0 (Noldus, Netherlands) allows saving the trajectory in the form of a set of coordinates. Coordinate registration was carried out at a frequency of 12.5 frames per second.

In the first four days of the experiment, the voles were trained to find a platform (9 × 9 cm) hidden under water, which was always located in the same place at a distance of 30 cm from the pool wall. Throughout the training, the location of the platform was not changed (although it could have been different for different animals). Such a protocol corresponds to the test version intended to estimate long-term spatial reference memory (Morris, 1984). The starting point was changed trial-by-trial according to the a random sequence. The interval between trials was at least 30 min. If the animal was not able to find the platform within 60 s, it was gently guided to the platform with the help of a lift net. The vole was left on the platform for 30 s. On the third and fifth day of the experiment, probe trials with the platform removed for 60 s was held before training. The probe trials allowed us to reveal whether the animals use distant visual reference points searching for the platform (spatial strategy) or other search strategies (e.g., memorizing the platform distance from the wall and swimming in circles). To detect possible motivational, motor, or sensory impairments on the last, 5th, day, the experiment was carried out using the cue version of the test (Morris, 1984). In this case, the platform was hidden under the surface of the water, but its position was labeled with a visual cue, that is, a flag located above the water level. The platform positions and the starting points were changed trial-by-trial.

Analysis of the recorded trajectories was performed using the facilities provided by the EthoVision system. In addition, the trajectories were exported to WinTrack (Wolfer et al., 2001) and their parameters were calculated.

The following parameters were calculated for each trial (except for the probe ones): path length (m), latency (time taken to reach the platform, s), the swim path efficiency index (%, the percentage of the path that differs by less than 15° from the target direction), the percentage of the path parallel to the pool wall (%), average velocity (m/s, not including episodes of immobility and those of movement with the speed <5 cm/s). Parameters such as the percentage of time spent in each of the four quadrants of the pool (in the target one where the hidden platform was previously positioned, in two adjacent quadrants to it, and in the opposite one), and the number of crossings over the 30-cm zone, where the platform was located (to calculate the indicator, the program EthoVision was used), were assessed in the probe trials.

The statistical analysis of the data was performed using STATISTICA 6.0. The significance of differences was assessed by the use of Student's *t*-test and analysis of variance (repeated measures ANOVA, the factors were "number of trials" and "group").

The experiments were performed in accordance with the Directive 86/609/EEC of November 24, 1986.

Spatial learning parameters in voles

Parameter	Day	Control	Caudal hippocampus lesion
The swim path efficiency index, %	1	15.2 ± 1.4	13.6 ± 0.8
	2	31.6 ± 2.3	21.1 ± 1.7*
	3	31.7 ± 2.2	25.2 ± 2.3
	4	35.4 ± 1.9	27.2 ± 2.4*
	5	40.8 ± 2.2	44.4 ± 2.7
The percentage of path parallel to the wall, %	1	30.8 ± 1.7	29.4 ± 1.8
	2	25.2 ± 1.4	23.8 ± 1.9
	3	21.5 ± 1.4	20.6 ± 1.7
	4	20.5 ± 1.2	24.0 ± 2.2
	5	21.6 ± 1.2	18.6 ± 1.5
Average velocity, m/s	1	0.25 ± 0.01	0.23 ± 0.01*
	2	0.27 ± 0.01	0.27 ± 0.01
	3	0.28 ± 0.01	0.27 ± 0.01
	4	0.27 ± 0.01	0.28 ± 0.01
	5	0.28 ± 0.01	0.29 ± 0.01

Note: * The differences between the control and experimental groups are estimated using Student's t-test ($p < 0.05$).

RESULTS

Histological examination showed that the lesion selectively covered the caudal part of the hippocampus, which includes the fields of Ammon's horn and the dentate gyrus. Some animals had the cortex parts, which lie above the hippocampus, slightly affected, but the rostral hippocampus was preserved in all cases. The first signs of cell damage were observed beginning from the level of −1.2 mm (caudal from bregma). Lesion of the CA3 region (cornu ammonis region 3) field and dentate gyrus was found in all animals at the level of −1.4 mm. The hippocampus was completely destroyed at the level of −1.8 mm, except for a small area in the dorsal CA1 (cornu ammonis region 1). The destruction extended over all areas of the hippocampus at more caudal levels. The calculation of the hippocampal lesion size showed that the voles had an average of 25 to 35% of the hippocampus lesioned in the caudal pole region (Fig. 1).

Voles in the experimental and control groups learned the Morris water maze with varying degrees of success. The path length and latency to locate the platform were reduced during the experiment in the voles from both groups (Figs. 2a, 2c). Hereby, the swimming speed was increasing (table). The repeated ANOVA measurements (analysis of variance with factors "number of trial" and "group") of dynamics of learning (Figs. 2b, 2d) over the factor "number of trial" showed the differences between these indices of performance to be significant (path length $F_{(19)} = 12.7$, $p < 0.001$, latency $F_{(19)} = 18$, $p < 0.001$, swimming velocity $F_{(19)} = 8.4$, $p < 0.001$).

The parameters that characterized the search strategy were changed as well. The swim path efficiency index, used to measure the efficiency of the swim paths to reach the goal location, was increased during training, while the percentage of the swimming path parallel to the walls of the pool decreased (table). Analysis of variance over the factor "the number of trial" has proved the significance of these differences (the swim path efficiency index $F_{(19)} = 6.02$, $p < 0.001$, the percentage of the swimming paths parallel to the walls of the pool $F_{(19)} = 7.1$, $p < 0.001$).

Despite the fact that animals from both groups were more successful at finding the platform during latter trials than during the first ones, the voles from the lesioned group compared with those from the control group took more time to reach the platform and their average swimming path was longer (Fig. 2). The platform search was less purposeful in lesioned voles. This fact is indicated by the decreased swim path efficiency index (table). Analysis of variance over the factor 'group' has proved the significance of the differences in latency ($F_{(1)} = 4.6$, $p < 0.05$) and the swim path efficiency indices ($F_{(1)} = 7.5$, $p < 0.05$). Interaction between the factors "group" and "number of trial" was not found.

The voles from both groups during the first probe trial preferred to search for the platform in the target quadrant (Figs. 3a, 3b). However the hippocampus

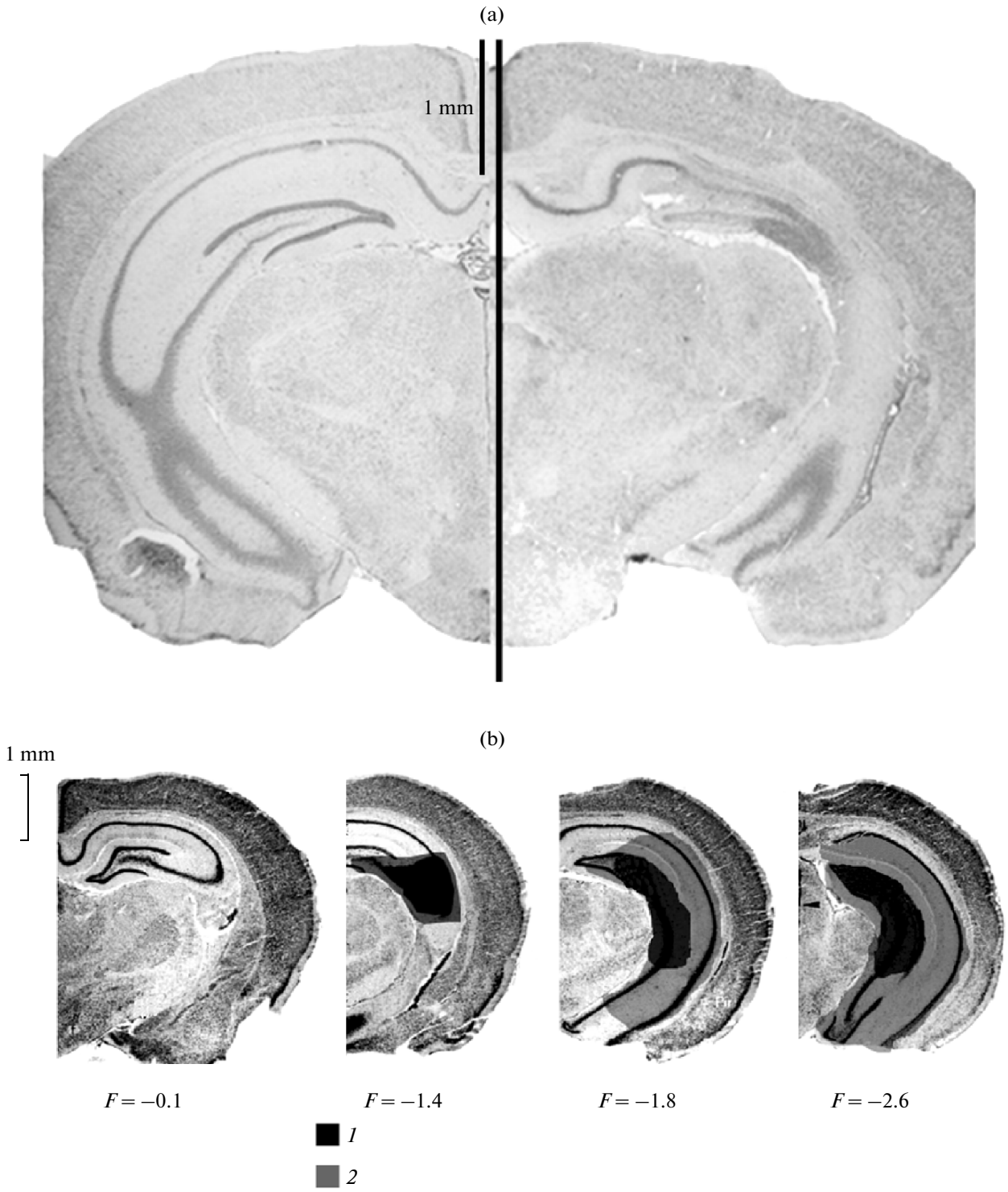

Fig. 1. Structural impairment in the vole hippocampus after a lesion of its caudal part: (a), brain slice with the hippocampus lesion at 1.6 mm caudal to bregma (right), a similar slice of the control vole (left); (b), the minimum (*1*) and the maximum (*2*) sizes of the lesion at several rostrocaudal levels (*F*—the distance from bregma, mm).

lesion resulted in decreased search accuracy. The number of crossings over a less extensive zone around the platform was decreased for the experimental animals in comparison with the control ones (Figs. 3b, 3d). This trend was observed during the second probe trial, but the difference was not significant.

The characteristics of learning worsened in the control voles on the second trial as opposed to the first

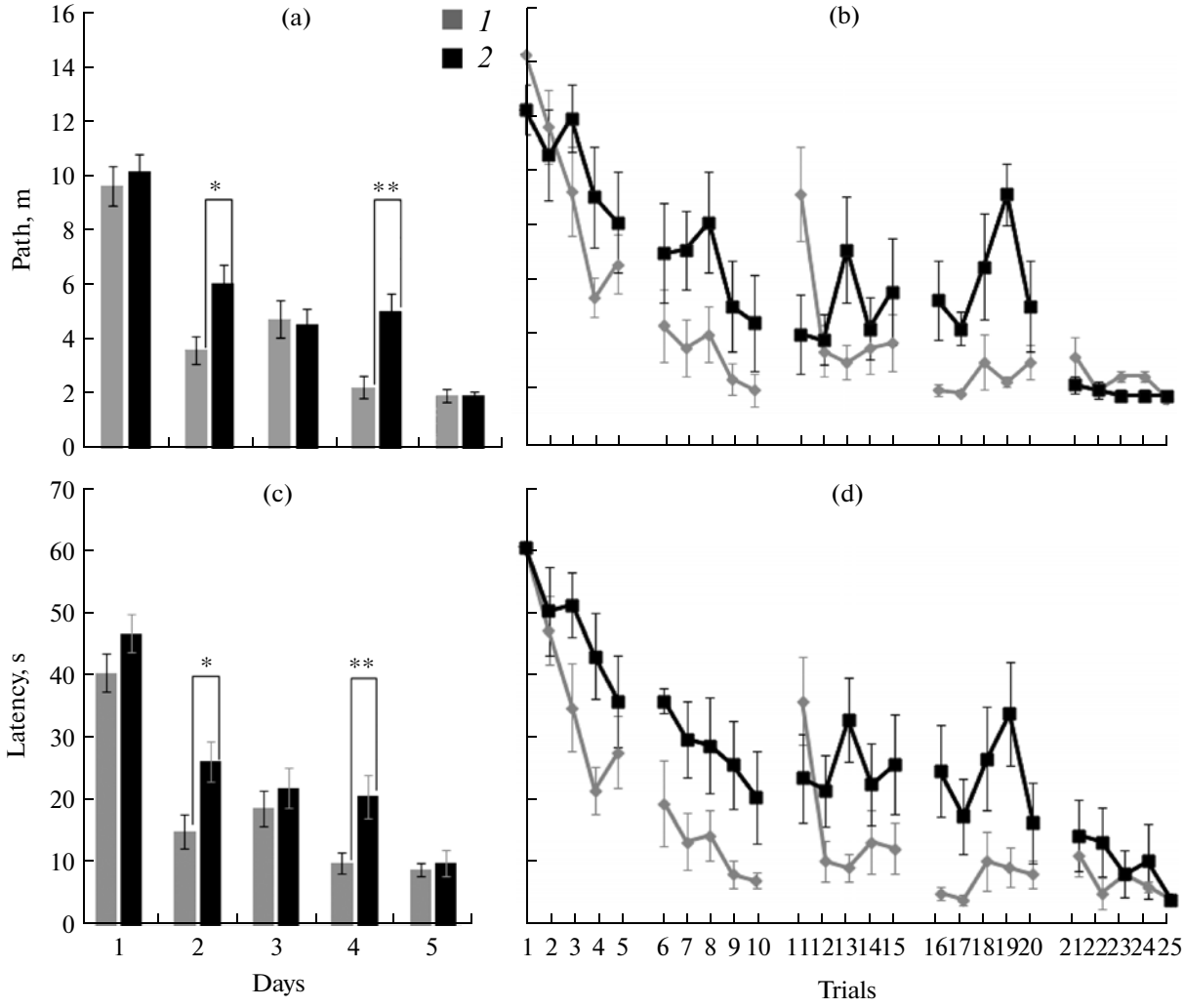

Fig. 2. Time history of the parameters characterizing learning of voles in the Morris water maze during the experiment: the length path versus the day of the experiment (a) and versus the distinct trial (b); the latency versus the day of the experiment (c) and versus the distinct trial (d). The differences between the control and experimental groups are estimated using Student's *t*-test. * $p < 0.05$., ** $p < 0.01$. (*1*), Control animals, (*2*), experimental ones, error bars indicate SEM. For Figs. 2, 3.

one. Thus, the path length and latency increased as compared with the first probe trial ($t = 5.08$, $p < 0.05$ (Fig. 2a) and $t = 4.3$, $p < 0.05$ (Fig. 2c), respectively; here and further Student's *t*-criterion is used). The swim path efficiency index decreased from 35.2 ± 5.5% to 17 ± 2% ($t = 3.8$, $p < 0.05$). However, on the next trial, these indices had the same values as they did before the test. The behavior of the voles with a caudal hippocampal lesion was not affected by the first probe trial.

Therefore, although the voles of both groups learned to find the hidden platform faster in comparison with the first trials, the caudal hippocampal lesion negatively affected the performance in the Morris water maze slowing the rate of learning.

The cue version of the water maze task revealed no differences between the groups.

DISCUSSION

The data obtained earlier (Pleskacheva et al., 2000) was confirmed by successful learning of the control voles in the experiment. The caudal hippocampus lesion affected the behavior of the voles, and thus, the latency and path length increased. Similar behavior was observed in rats with the entire hippocampus removed (Morris et al., 1982). However, complete lesion of the hippocampus had a larger effect than partial removal. The experimental voles searched for the platform in the probe trials with less accuracy than the control ones, though they did it in the target quadrant, while in Morris' experiment (Morris et al., 1982) the target quadrant was not preferred by the experimental rats.

The data obtained reveal spatial learning impairments in rodents with a lesion of the caudal part of the hippocampus, which does not comply with the con-

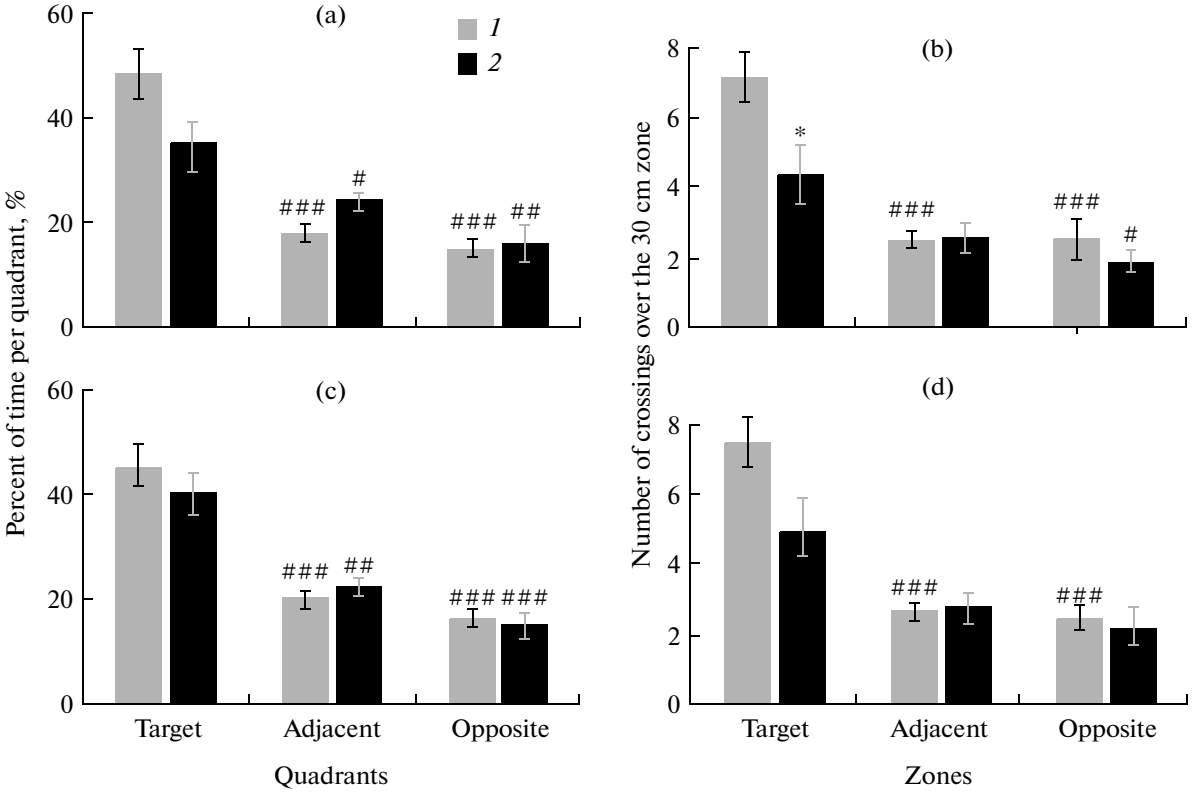

Fig. 3. The parameters of the probe trials: the percentage of time spent in the target quadrant (a) and the number of crossings over the 30-centimeter zone (b) in the first probe trial; the percentage of time spent in the target quadrant (c) and the number of crossings over the 30-centimeter zone (d) in the second probe trial. The differences between the control and experimental groups are estimated using Student's *t*-test. * $p < 0.05$. The ones found comparing with the target quadrant: # $p < 0.05$., ## $p < 0.01$., ### $p < 0.01$.

clusions made by other researchers. Most studies performed on rats with similar partial hippocampal lesion do not demonstrate such an effect on the learning of rats in the Morris water maze (Moser et al., 1993, 1998; Bannerman et al., 1999; Richmond et al., 1999). However, it should be noted that impairments observed in the probe trial of our experiment can be revealed only by evaluation of the search in the zone around the platform, not in the whole quadrant. Perhaps such an approach could have revealed impairments in rats as well. Moreover de Hoz and colleagues (de Hoz et al., 2003) have demonstrated that the rats with the hippocampus spared search for the platform in the probe trial held after 4 days of training with less accuracy than control rats. In the second probe trial held in the original research (Moser et al., 1995), this difference disappeared, as it was not observed in our study in the voles. Finally, the figure shown by Moser et al. (Moser et al., 1993) demonstrates that rats with the caudal hippocampus lesioned learned more slowly than control rats, though this effect is not so obvious as that observed in our experiment (there are no data reported on its statistical significance).

To examine the search strategy, the criterion of the search efficacy calculated using Wintrack (Wolfer et al., 2001) was used. It allowed us to identify impairments of the intentional search in the animals with the lesion of the caudal hippocampus. Such an analysis has not been carried out in other studies (Moser et al., 1993, 1995).

Therefore, the results obtained as well as findings noted by other investigators indicate the possible involvement of the caudal hippocampal region in the spatial learning of the Morris water maze task when long-term reference memory is measured. This is also confirmed by the effect of the caudal hippocampus lesion on the working memory in the other version of the Morris water maze task (Ferbinteanu et al., 2003; Bast et al., 2009).

These findings could have two possible explanations. The first of them is that the lesion of the caudal hippocampus leads to loss of the place cells with large receptive fields. Presumably such cells provide low-resolution spatial information coding (Kjelstrup et al., 2008; Moser et al., 2008). It is indirectly confirmed by the fact that every rat in the sole investigation that earlier (de Hoz et al., 2003) revealed impairments (the reference memory task) was trained using two different protocols and in two different pools, and rats were supposed to distinguish them. It can be thought that such recognition requires a perfect spatial coding system.

The second explanation follows from the peculiarities of the connections between different parts of the hippocampus and other structures. For instance, the hippocampal caudal region is connected with the prefrontal cortex (Ferino et al., 1987) and the neurons of the latter are believed to form a single network with pyramidal cells of the hippocampal rostral part through the connections running along the longitudinal axis between different rostrocaudal levels of the hippocampus (Amaral and Witter, 1989). Such a network appears to be involved in planning of animal movement trajectories (Hok et al., 2007).

Lesion of the caudal hippocampus results in disrupted connections that could result in an search efficacy. The impaired trajectory planning mechanism seems to mostly affect the parameters that characterize the dynamics of learning (e.g., the swimming path efficiency index allows evaluation of search strategy) and with this reveal the ability of an animal to reach the platform using the optimal trajectory. The probe trial allows estimation of the already developed skill to reach the platform, and its indicators do not describe the difficulties in learning at early stages. It is indirectly confirmed by the fact that removal of the prefrontal cortex influences the dynamics of learning in the Morris water maze task, but not the parameters of the probe trial (Silachev et al., 2009). A similar explanation was also considered by investigators referring to the same hypothesis of the interaction between the hippocampus and the prefrontal cortex (Bast et al., 2009). Bast et al. (2009), taking into account the intermediate region of the hippocampus largely overlapping with the area removed in our experiment, believe it to convert information in hippocampus into signals that regulate behavior. However, the researchers applied the hypothesis only to tasks connected with spatial working memory. We believe a similar mechanism to be engaged in performance of long-term spatial reference memory tasks.

The caudal hippocampus lesion negatively affects learning of voles in the Morris water maze; however, this effect is weaker than that observed after the removal of the rostral part of the hippocampus (Moser et al., 1993, 1995; Bannerman et al., 2004). Searching for a hidden platform takes more time. That is not caused by the slow swimming velocity and, therefore, does not result in an increased swimming distance. Having used a wider range of scores than is usually done in similar investigations, we were able to discover new facts that were not reported by other scientists in experiments on rats (Moser et al., 1993, 1995; Bannerman et al., 2004). We demonstrated that a caudal hippocampus lesion reduces the search accuracy and target-oriented behavior.

The absence of impairments in the cue version of the task proves that the motivation to find the hidden underwater platform marked by a flag as well as the basic motor and visual functions are preserved in the animals; i.e., the impairments revealed in our experiment are specifically related to the spatial task requirements (searching for the hidden platform using distant visual reference points).

The experiments carried out on voles confirm and supplement the data collected by other researchers for rats (de Hoz et al., 2003; Ferbinteanu et al., 2003; Loureiro et al., 2011).

CONCLUSIONS

The results of our experiments show that the caudal part of the hippocampus is involved in the regulation of spatial learning. However, the nature of the involvement in the process needs to be refined. It is possible that the effects observed after the caudal hippocampus lesion are caused by an impairment in the formation of full spatial representation in the hippocampus which results from damage to place cells coding spatial information at low resolution. This does not exclude the other possible hypothesized cause of the damage, which is disruption of the hippocampal-prefrontal network involved in trajectory planning. The data obtained, as well as the results of our previous investigations concerning functioning of the caudal part of the hippocampus, demonstrate that this area plays a crucial role in the control of spatial behavior and there are prospects for further research in this direction.

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