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Physiology & Behavior, Vol. 60, No. 3, pp. 895–900, 1996

0031-9384/96 $15.00 + .00

PII S0031-9384(96)00101-1

Septal Lesions Impair Rats' Morris Test Performance But Facilitate Left–Right Response Differentiation

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Received 17 October 1995

NOONAN, M., M. PENQUE AND S. AXELROD. *Septal lesions impair rats' Morris test performance but facilitate left–right response differentiation.* PHYSIOL BEHAV **60**(3) 895–900, 1996.—Lesions in the septum impaired performance on the Morris test, a task in which the rat locates a hidden escape platform by use of fixed landmarks, but facilitated a water maze-based left–right response differentiation, a task in which the rat finds a hidden escape ramp by means of its internal sense of direction. These results are interpreted as supporting an allocentric/egocentric dichotomy with respect to navigation, and support the notion that rats approach spatial problems with a hierarchy of potential solutions in which allocentric solutions take precedence over egocentric ones. The septal lesions are inferred to disrupt the allocentric mapping system.

Septal lesions Spatial learning Rat Water maze Left–right learning Allocentric Egocentric Navigation

IT IS now well established that lesions of the septal–hippocampal axis disrupt an animal's ability to master spatial navigation tasks, particularly those that are approached with what O'Keefe and Nadel (22) call a "place hypothesis." Lesions to the lateral septum (11), medial septum (2,3,5), fornix (16,23), and hippocampus (15,27), and/or chemical disruptions of the interconnections among these structures (9,17,24), are particularly disruptive to animals that attempt to solve a spatial problem by forming an allocentric, "cognitive map" of their surroundings.

By contrast, the distinction between left and right should not, indeed cannot, depend on a place hypothesis. The left–right difference is an *egocentric* one that changes its relationship to the surroundings as the animal moves about. That is, the directions left and right orient an animal towards different places in its environment depending on which direction the animal is facing at any given moment. One might expect, therefore, that an animal's ability to distinguish left from right would be independent of its ability to form a cognitive map, and so would be unimpaired by lesions in the allocentric mapping system.

An animal's ability to distinguish left and right can be tested directly in what Corballis and Beale (1) call a "left–right response differentiation" task. Here an animal is obliged to differentially associate mirror-image responses (such as turning left and turning right) with arbitrary stimuli that do not contain any inherent directional mirror-image information (e.g., lights on/lights off). O'Keefe and Nadel (22) reviewed some experimental tasks that would appear to fit these criteria in their discussion of "successive discriminations" (p. 284). Although recognizing that such tasks do not depend on cognitive mapping, they nevertheless reviewed experimental findings that performance on such tasks has, in some instances, been impaired following damage to the putative mapping system. To account for this, they speculated that animals with impaired mapping abilities might be compelled to adopt maladaptive orientations on such tasks. In their discussion, O'Keefe and Nadel cited studies in which hippocampus-lesioned rats were deficient at food-motivated, successive discrimination tasks requiring them to turn in one direction when the maze walls were black and the opposite direction when the maze walls were white (4,7). In these studies the hippocampal rats had adopted persistent habits in which they turned in only one direction for long strings of trials. The more recent work of Marston, Everitt, and Robbins (10) may also be relevant here because they too employed a task that might have been approached by their subjects as a left–right problem. They found that septal lesions resulted in deficiencies on a "conditional visual discrimination" in which rats in operant chambers were obliged to press the left lever when lights flickered at one frequency and the right lever in response to a different frequency.

However, none of these studies were designed to focus specifically on the allocentric/egocentric distinction vis-à-vis spatial navigation. Accordingly, their left–right tasks were not designed to minimize allocentric cues, nor were any efforts included to confirm that their subjects solved their tasks by critically distinguishing left and right. In the hippocampal studies (4,7), the rats

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were tested in mazes that were fixed in place within well-lit rooms possessing salient extra-maze landmarks, and operant chambers like the ones used in the Marston et al. study (10) likewise typically contain observable stationary features. As O'Keefe and Nadel themselves argue, rats appear to try to solve spatial tasks preferentially using place-based, allocentric mapping, particularly when salient fixed landmarks are available. It is at least possible that the rats in these studies were influenced by the fixed features of their testing environments, and made inappropriate attempts to associate the location of reward with these features.

Unfortunately, this has left us without a clear experimental demonstration of the effects of lesions of the septal–hippocampal axis on an animal's ability to make the distinction between left and right, and, more generally, without an unequivocal test of the dissociability of egocentric left–right response differentiation from the allocentric mapping system. We are left with the unsatisfying speculation (22) that lesioning the allocentric mapping system impairs not only performance on tasks demanding navigation to fixed places by means of extra-maze cues, but also performance on tasks demanding egocentric orientations independent of fixed cues because the orientation system becomes maladaptively engaged. Our goal in this project was to try to resolve this situation by testing the effects of septal lesions on a task specifically designed to test the animal's ability to make the left–right distinction.

In our laboratory, we have been investigating the behavior of rats in a left–right response differentiation (LRRD) task using a water escape variation on the theme (18–21). We test our animals in a pair of M-shaped tanks oriented in opposite directions in different dimly lit rooms, which we have endeavored to keep as symmetrical and featureless as possible. Over successive trials, the rats learn to swim to the right under one nondirectional stimulus condition and to the left under another such condition. By testing the performance of rats under different probe conditions after they have mastered this task, we have shown that our subjects continue to show reliable left–right response differentiation when their testing is carried out in the alternative maze oriented in the opposite direction. That is, we have a test in which the salience of allocentric mapping cues is minimized, and on which we have earlier demonstrated that rats solve the problem posed by means of egocentric navigational reference.

Our goal was to examine the effects of lesions in the septum on the ability of rats to distinguish left and right in our paradigm, and to contrast the results with the effects of the lesions on the most common behavioral test of allocentric cognitive mapping—the Morris test (13,14). In this task, the rat swims repeated trials in a tank of water in search of a submerged refuge platform. From trial to trial, the rat is placed into the tank at varying locations, and comes over time to efficiently locate the platform in its fixed location by means of noting its position relative to salient landmarks outside of the tank.

METHOD

Subjects

Ninety-eight adult male and female hooded (Long–Evans) rats were maintained on an alternating 12:12 white:red light cycle. Room temperature was kept at 26°C.

Surgery

The rats were randomly assigned to one of three surgical treatments. The septal group ($N = 33$) sustained bilateral electrolytic septal lesions. Animals in the sham group ($N = 34$) experienced electrode placement but no current. Animals in the intact group ($N = 31$) were anesthetized, positioned in the stereotaxic head holder, and subjected to scalp preparation, but no skull or brain defects were created. Because the septal electrodes of the first two groups passed through the corpus callosum, and we have shown in earlier studies (20,21) that callosal damage can itself facilitate LRRD, we included the intact group as a basis for comparison with our sham group to assess the degree to which the electrode passage itself contributed to our findings.

Anesthesia was accomplished through IP administration of ketamine (Ketaset, 52 mg/kg) combined with xylazine (Rompun, 2.6 mg/kg). The subject was mounted in the flat-skull position [i.e., nose-clamp at −3.3 mm (25)] and the tip (uninsulated for 1 mm) of a monopolar electrode (0.8 mm diameter) was lowered under stereotaxic guidance through 2-mm bore holes to points 0.5 mm anterior and 0.6 mm lateral to bregma, and 6.6 mm ventral from the surface of the skull. For the septal subjects, 2.0 mA of current was passed into the septum on each side for 7.5 s. The reference (negative) was a clip attached to the edge of the open scalp.

For logistical reasons, the rats were divided into three cohorts, counterbalanced with surgical groups, which commenced behavioral testing 6, 8, and 10 weeks postsurgically. In the week preceding testing, the rats were handled twice daily to habituate them to human contact. Each rat underwent LRRD testing first and the Morris test 1 week later. All animal handling and data collection were carried out by observers blind to the animals' surgical group assignment, and recorded on videotapes that were then reviewed by a second blind observer.

LRRD Test

We employed two M-shaped Plexiglas water mazes, 46 cm deep [cf. (20)]. Water entered continuously (6.3 l/min at 24°C) at the floor of the starting box, and flowed out at the floor at the ends of both arms, being maintained at a depth of 25 cm. Each maze arm was 15 cm wide and extended for 30 cm laterally. The arms then turned 90° back, so that an escape ramp, extending down into the water at the end of the appropriate arm, was out of sight to the rat at the choice point. The reinforcement was escape from the water, accomplished by climbing up the ramp.

Testing took place under red light. The walls of the maze were white and could be back-illuminated. When not illuminated, the walls as viewed from within the maze appeared to the human observer as uniform and dark. When back-illuminated, alternating dark and light 3-cm-wide vertical stripes appeared. On trials in which the maze walls were illuminated, the escape ramp was always placed in the right arm; when the walls were unilluminated, the escape ramp was in the left arm. A "dummy" ramp, which extended down only to 15 cm above the water surface and could therefore not be used for escape, was always placed in the opposite arm so that the escape ramp location could not be determined by a view from outside the tank.

Pseudorandomly sequenced trials (maze illuminated/maze unilluminated) were presented at 4-min intertrial intervals. On each trial the rat was placed in the starting box and allowed to swim until it found the ramp; it was then returned to its home cage until the next trial. Each rat was tested for 25 trials per day until it reached the criterion of 10 successive correct first turns at the choice point, or for a maximum of 5 successive days. The number of trials taken to reach criterion served as the index of difficulty in making the left–right response differentiation [cf. (18–21)].

Seven rats (zero septal, three sham, four intact) failed to reach criterion after completing the 5 days of testing (125 trials); they

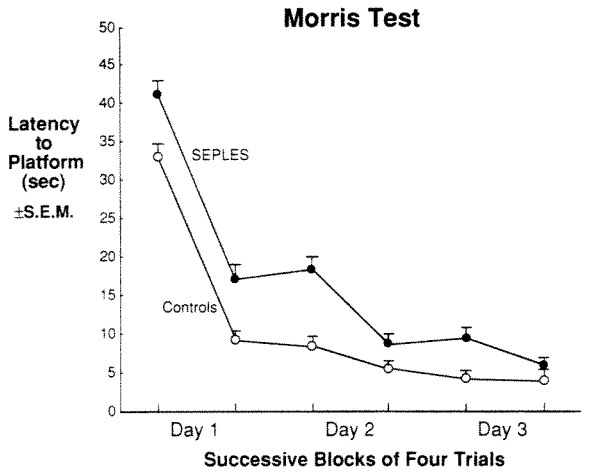

FIG. 1. Mean escape latency in four-trial blocks on the Morris Test, by group.

were assigned trials-to-criterion scores equivalent to the lowest score possible given their ending performance. As examples, if the response on the 125th trial was the last of five consecutive correct responses, the rat was given a score of 130. If the 125th trial was incorrect, the rat was given a score of 135.

In this study, as in related projects, we conducted 10 additional trials to confirm that our subjects' scores were not functions of confounding variables. After initially reaching criterion, each rat was moved temporarily into an adjacent hallway and then moved either into a different room to be tested by different experimenters in a maze oriented differently with respect to compass heading, or back into their original testing room for 10 additional trials under conditions identical to their initial training. The rats in the latter condition served to provide a basis of comparison to allow us to assess the influence on the rats of being moved about.

Morris Test

For this test, the rats were moved to a room illuminated by white lights. We employed a cylindrical polyethylene tank 140 cm in diameter and 45 cm deep. It was filled with 26°C tap water to a depth of 21 cm. An inverted clear-glass jar (11 cm diam, 20 cm high) served as a hidden refuge platform just under the surface of the water. For any given rat, the platform was always located centrally in a particular quadrant of the tank, with this escape quadrant being varied from rat to rat, counterbalanced across groups. For eight trials per day over 3 successive days, the rat was placed into the tank facing the near tank wall, with the entry quadrant varying randomly within the provision that each quadrant was included in each block of four trials. The latency for the rat to reach the refuge platform was recorded for each trial. If on any trial the rat had not reached the platform after 120 s, it was placed on the platform by hand. In either case, the rat was left to stand on the platform for 20 s after reaching it.

In other laboratories that employ the Morris test, a white powder is commonly added to the tank water to reduce the visibility of the platform [e.g., (2,15,27)]. We satisfied ourselves that such a procedure to hide the location of our glass platform was unnecessary for the following reasons: a) a human observer has difficulty finding the transparent platform when viewing from any angle; b) the platform becomes visually unavailable as the point of view approaches the surface of the water (i.e., because of the viewing angle, the "rat's-eye view" of the water's surface reveals only reflections of above-water stimuli); c) the rats often swam within a centimeter of the platform without detecting it; d) on the day following the 3 standard days of formal testing described above, we conducted trials on some rats in which no platform was present, and found that the latency to swim to the previously trained quadrant was not different from the latency on trials in which the platform was present; and e) on day 4 test trials on other rats, we placed the platform in "incorrect" (i.e., not previously reinforced) quadrants and found that the rats swam with unchanged latency to the previously reinforced quadrant, and then initiated search patterns that were as often directed toward either of the other empty quadrants as toward the one with the platform.

Histology

Following behavioral testing, the rats were perfused intracardially with saline followed by formalin. Serial 8-μm coronal sections were made, and every 20th slice was stained with cresyl violet.

RESULTS

The performances of the sham and intact rats were very similar and not significantly different on either behavioral test; these

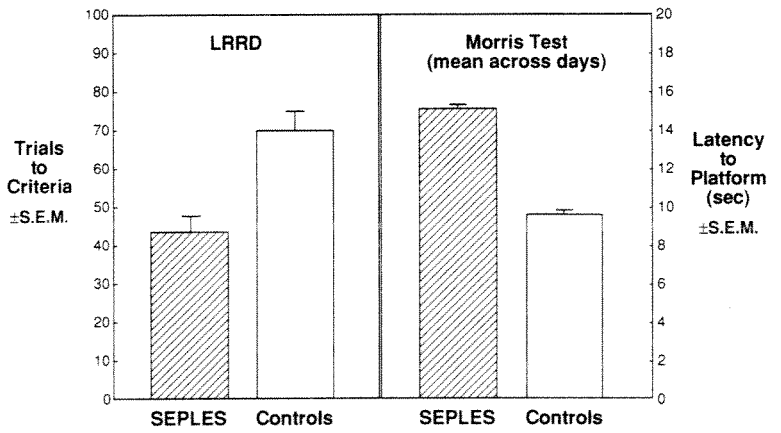

FIG. 2. Performance on the left–right response differentiation (left) and Morris (right) tests.

FIG. 3. Brain sections from a representative subject. The entire septal complex is destroyed (including the lateral, medial, and triangular subdivisions) with consequent ventriculomegaly. Secondary atrophy of hippocampal–fimbrial fibers is also evident.

groups were therefore combined into a single control group for subsequent analyses. Similarly, there were no cohort differences on either task, nor were there any significant statistical interactions between cohort and surgical groups. Accordingly, in the analyses presented below the cohorts are combined.

As expected, the septal subjects were substantially impaired in mastering the Morris test (see Figs. 1 and 2). The mean latency of the lesioned group to reach the platform (mean = 15.4 s) was 58.8% higher than that of the controls (mean = 9.7), $F(1, 94) = 37.6$, $p < 0.0001$. When examined separately by four-trial block, this impairment of the septal group was statistically significant ($p < 0.01$) for each of the blocks except the last. The sexes did not differ in overall mean latency, $F(1, 94) = 0.0$, NS. However, there was a marginally significant interaction between surgical treatment and sex, $F(1, 94) = 3.9$, $p = 0.053$, reflecting the fact that the magnitude of the impairment of the septal animals compared to controls was greater for males than for females.

By contrast, on the left–right response differentiation task, the septal subjects were dramatically *superior* to the controls (Fig. 2, left panel). The trials-to-criterion scores for the lesioned subjects (mean = 43.1) averaged 38.4% lower than those of the controls (mean = 70.0), $F(1, 94) = 22.0$, $p < 0.0001$. The sexes also differed significantly, $F(1, 94) = 7.9$, $p = 0.006$, females overall having lower scores than males. The statistical interaction between sex and surgical group was not significant. In the 10 postcriterion trials conducted after the rats were moved, rats from both surgical groups and in both postcriterion testing conditions continued to demonstrate reliable left–right response differentiation.

In an effort to assess whether the lesioned rats were more prone to adopting maladaptively persistent orientations on this task, we tabulated for each subject the total number of trials spent in a string of consistently directed first responses at the maze choice point. That is, we counted the number of consecutive trials on which the rat turned left, and similarly the number of consecutive trials on which it turned right. For this purpose, we included in a string any trial whose first response was in the same direction as the one before and/or after it, so long as at least one of the responses in the string was incorrect. We also tabulated the number of times there was a break in such behavior, and the number of times the rat switched from a left-going string to a right-going string or vice versa. We then expressed these totals as proportions of the total number of trials. Overall, the septal subjects averaged *fewer* of their trials in such unilateral strings than did the controls (54% vs. 64%, respectively), and this difference proved statistically reliable, $F(1, 96) = 9.68$, $p = 0.002$. The groups did not differ in the number of breaks in their strings nor in the number of switches in direction from string to string.

Microscopic examination of the brain sections of the septal group revealed lesions confined to the septal region with the corpus callosum, caudate/putamen, hippocampus, and thalamus essentially normal in appearance in each subject. Across subjects there was some variation in the anterior/posterior extent of the lesion. In 14 subjects, the lesions were largely confined to the lateral and medial septal subdivisions with little or no involvement of visible fimbrial fibers or the triangular septal nucleus. In the other 19 septal subjects, the lesions extended posteriorly to include much of the anterior fimbria and triangular nucleus. Brain sections from a representative subject of this latter type are presented in Fig. 3. For each subject, in a process blind to the behavioral results, we visually estimated the percentage of tissue in each septal subdivision that remained, and we subsequently assessed the relationship between these estimates and the rats' behavioral scores. There was a significant positive correlation ($r = 0.55$, $p < .01$) between the proportion of fimbria and triangular nucleus damage and overall mean latency to reach the refuge platform in the Morris test—the more posterior the lesion, the worse the performance in the Morris test. However, direct fim-

brial involvement did not appear to be critical in explaining the septal group's collective impairment on the Morris test. An analysis of variance comparing the mean escape latency of the 14 subjects in which the fimbria was largely spared with that of the combined control subjects showed that lesions confined to the lateral and medial septum were alone sufficient to significantly impair Morris test performance, $F(1, 77) = 12.9, p = 0.001$. No statistically reliable relationships were obtained between LRRD scores and any of these post hoc assessments of damage to septal subdivisions.

DISCUSSION

The impairment shown by our septal-lesioned rats on the Morris test replicates similar findings and confirms a role for the septum (2,5,10,12,17), along with that shown by others for the hippocampus (10,15,22,28), in the conduct of landmark-guided spatial navigation. The marginal sex by surgical group interaction we found is compatible with the notion that male and female rats may engage the spatial mapping neural substrate differently (29).

It remains to be asked whether the septal–hippocampal axis comprises a single functional system with respect to spatial navigation, such that lesions to any one critical component are as debilitating as would be a lesion of the whole. Alternatively, each subcomponent might make its own contribution in a way that remains somewhat functional in the absence of the others. Our findings appear to be compatible with the latter view: lesions that appeared to be restricted to the lateral and medial subdivisions of the septum were alone sufficient to produce a significant impairment on the Morris test, and even greater deficits were shown as the extent of lesion in the fimbria increased.

Regarding our left–right task, the sex differences we found in mean trials-to-criterion scores do not correspond to results from our earlier studies (18–21) in which the sexes were essentially equal in performance. We are therefore inclined to caution in attributing this finding to the population at large.

The possibility that the improvement in LRRD we are attributing to septal lesions might be due to incidental callosal damage must be considered. In other work we have shown that severing the corpus callosum leads to an improvement in LRRD scores (20,21), presumably by eliminating the intermixing of lateralized information. Nevertheless, three reasons make us inclined to rule out callosal damage in explaining our present results: a) microscopic examination of the stained sections from the septal brains showed no evidence of electrolytic damage in the callosum; b) the sham subjects, which also experienced electrode penetration through the callosum, did not differ significantly from the intact subjects; and c) although the possibility cannot be ruled out that the functioning of the adjacent callosal area was impaired in ways not evident upon microscopic examination, we have shown in other work (21) that when the entire anterior third of the corpus callosum (the area adjacent to the septum) is severed, the magnitude of the LRRD improvement is only 16.3% compared to sham operates, an effect much smaller than the magnitude of the improvement found here following septal lesions (38.4% improvement compared to controls). Indeed the improvement shown by the septal subjects is greater than that shown even by completely callosotomized subjects in the earlier study (30.5%). We therefore consider it unlikely that the facilitation of LRRD in the present study derives primarily, if at all, from impaired functioning of the callosum.

That the septal subjects were not deficient on the LRRD task is compatible with the view that the role of the septal–hippocampal axis in spatial processing is specific to allocentric cognitive mapping by means of external landmarks. Clearly, because our lesioned subjects were not impaired at our LRRD task, the integrity of the septal–fimbrial region is not a necessary precondition for all types of spatial learning.

That the septal animals in this study were actually substantially superior at the LRRD task contrasts with the normal expectation that brain damage would result in behavioral deficits. However, this finding is not without precedent. For example, septal lesions in rats also facilitate learning of shuttlebox active avoidance [e.g., (6,8,26)]. Such results are compatible with the notion advanced by O'Keefe and Nadel (22) that animals follow a hierarchy of hypotheses when approaching a spatial problem, and ordinarily first approach problems containing spatial elements by attempting to map relevant stimuli relative to fixed landmarks. Thus, rats in a shuttlebox by natural inclination first try to learn the location of the safe place. It is only after they have exhausted this spatial mapping strategy as a potential solution that an approach lower in the hierarchy is adopted. On this view, when intact rats encounter our LRRD task they ordinarily expend some initial trials attempting to map the new environment and trying to remember where in a fixed spatial framework the escape ladder is reliably located. Only after this process is determined to be futile—a step facilitated by the unavailability of fixed landmarks—do the subjects entertain the (correct) possibility that the ladder moves about and that its location can be predicted by the luminance of the walls. O'Keefe and Nadel (22) argue that when an animal's cognitive mapping system is impaired due to lesions in the underlying neural substrate, it more readily abandons the allocentric mapping strategy and shifts more quickly to alternative ones.

If the rats' adoption, in the initial stages of our LRRD task, of persistent tendencies to turn in one direction at the maze choice point is viewed as consequent to an attempt by the rats to identify one spatially fixed arm of the maze as the location for escape, then the fact that our normal rats characteristically adopt such position habits, and that our septal-lesioned rats were less likely to do so, is also compatible with the notion that animals approach such tasks initially with a cognitive mapping strategy, and that this strategy is either unavailable or less firmly exhibited at the top of the hierarchy when its neural substrate is impaired. According to this view, it is precisely because our septal animals were deficient at allocentric cognitive mapping that they were facilitated at egocentric left–right response associations.

ACKNOWLEDGEMENTS

This work was supported in part by a grant to Canisius College from the Charles A. Dana Foundation, and by a grant to M.P. from Sigma Xi. The authors thank and praise Jill Krakowiak and Debra Lipczynski, who served as research assistants, and Sandra Thamer who provided histological processing.

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