Mediodorsal thalamus lesions in rats impair radial-arm maze performance in a cued environment

KATHRYN A. STOKES and PHILLIP J. BEST
University of Virginia, Charlottesville, Virginia

In a previous experiment (Stokes & Best, 1988), we showed that rats lesioned in the mediodorsal nucleus of the thalamus performed poorly on a radial maze placed in a visually deprived environment. The present experiment was designed to assess performance of similarly lesioned rats on the radial maze when extramaze cues were plentiful. Sixteen rats were trained on the radial maze; 7 then received electrolytic lesion of the mediodorsal thalamic nucleus. Despite excellent preoperative acquisition of the task, postoperative performance was severely impaired in all animals given lesions. These animals made more errors, and made errors earlier in the session, than did control animals. Furthermore, animals with lesions developed stereotyped patterns of responding on the maze, as had animals in the previous study. Thus, we replicated our previous findings with respect to the effects of lesions of the mediodorsal nucleus, and extended their generality to a more usual, visually enriched testing environment. Our results indicate that the impairment in maze performance subsequent to mediodorsal thalamus lesion is nonspecific, affecting memory secondarily.

Recent research has focused on the role of the mediodorsal nucleus of the thalamus (MD) in memory processes both in humans (e.g., Brown, Kieran, & Patel, 1989; Speedie & Heilman, 1983; Squire & Moore, 1979; Winocur, Oxbury, Roberts, Agnietti, & Davis, 1984) and in nonhuman species (e.g., Gaffan & Harrison, 1987; Kessler, Markowitsch, & Otto, 1982; Kolb, Pittman, Sutherland, & Whishaw, 1982; Mair, Anderson, Langlais, & McEntee, 1988). Results for the rat on spatial memory tasks have been equivocal, however. For example, Kolb et al. (1982) found animals with MD lesions to be unimpaired on the Morris water maze task and on their version of a radial maze task. Furthermore, Kessler et al. (1982) found only subtle effects of MD lesion on radial maze acquisition. A deficit appeared only when a delay was inserted between the fourth and fifth choices.

In contrast, we recently reported (Stokes & Best, 1988) an unexpectedly severe impairment of postoperative performance of a previously well-learned but difficult radial maze task in animals given MD lesions. Task difficulty was enhanced by placing the maze in a darkened and visually deprived environment. Rats given MD lesions not

only made more errors on the task than did control animals, but also displayed rigid response patterns. These patterns were minimally effective, since errors were not corrected on the basis of previous responses.

The present experiment was designed to test whether the severe debility and the rigid response patterning exhibited by the animals with MD lesions in the above experiment emerged because of the increased difficulty of a visually noncued radial maze task. Thus, the previous experiment was replicated and extended by using a radial maze placed in a visually cued environment.

METHOD

Subjects

Sixteen male Long-Evans hooded rats, obtained from Charles River Breeding Colony, were used in this experiment. Housing conditions and feeding schedules were as reported previously (Stokes & Best, 1988). All behavioral testing was conducted in the latter portion of the light cycle and was followed by access to food. Water remained available to the subjects at all times.

Seven of the rats received bilateral lesions of the MD nucleus; the 9 others served as controls. Of the control animals, 3 were included from another, related, experiment.

Apparatus

An eight-arm maze similar to the one described previously was used for behavioral testing. Briefly, the center portion of the maze was 25 cm wide, and each of the eight arms was 50 cm long and 9 cm wide. Each arm was walled with clear Plexiglas, 5 cm high, angled outward. Metal food cups, 1.5 cm in diameter, were placed at the ends of the arms, to hold the reinforcer. Confinement to the central area was accomplished using a remotely operated system of doors. The maze was situated in an equipment storage laboratory room that contained a plethora of extramaze visual cues, in-

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cluding shelves of equipment, a table, a closed cabinet, and the experimenter.

Handling and Adaptation

The animals were placed on a food-deprivation schedule 1 week prior to maze training. Each day, the subjects were handled, weighed, and allowed access to food (approximately 20 g per animal). The subjects were adapted to the reinforcer on Days 5 and 6 of deprivation. They received, in the home cage, pieces of "Froot Loops" cereal, placed in food cups similar to those found on the maze. The animals were introduced to the radial maze on Day 7. After being placed on the central platform, they explored the maze for 10 min and retrieved pieces of cereal strewn along the maze arms and in the food cups. A second session of exploration occurred the following day.

Preoperative Training

The animals were trained to run the radial maze with all eight arms baited following the 2nd day of adaptation. Daily trials, involving one traverse of the maze, were terminated after the subjects obtained all eight pieces of cereal (approximately 640 mg total food). Training was continued until each animal had undergone 30 preoperative trials. One trial was administered per day, 6 days per week.

Surgery

Mediodorsal thalamic lesions were performed under sodium pentobarbital anesthesia (45 mg/kg, i.p.), with prior injection of 0.2 ml (0.4 mg/ml, i.p.) atropine sulfate. Lesions were made with a 0.25-mm insect pin, insulated with epoxy to the tip, through which 1 mA of direct anodal current was passed for 25 sec. The following coordinates were used to locate MD, taken from the atlas of Pellegrino, Pellegrino, and Cushman (1979): 1.3 mm posterior to bregma, 0.75–1.0 mm lateral to the midline, and 5.5 mm ventral to the surface of the cortex. During recovery, the animals were monitored carefully for food and water intake. Four days of postoperative recovery were allowed prior to reexposure to the radial maze task. At this time, all animals were eating and drinking normally (although this was not systematically measured).

Postoperative Testing

The animals underwent 30 postoperative trials following recovery from surgery. These trials were conducted as in presurgical training. Measures recorded included total number of errors and the pattern of arm entry chosen by each animal on each trial.

Histology

Upon completion of testing, the subjects were sacrificed with an overdose of anesthetic and were perfused intracardially with nor-

Figure 1. Representative lesion for animals in the present experiment. The mean amount of damage inflicted on the medial thalamus and other structures is presented at several levels throughout MD. Lesions tended to be large, yet were restricted to the medial thalamic area, with only slight involvement of the hippocampus along the midline. See text for further details.

mal saline followed by 10% formalin. The brains were extracted, soaked in 30% sucrose formalin, and then sectioned at 40 μ and stained with cresyl violet. The lesion area was reconstructed and damage outside the MD nucleus noted. Representative lesions were drawn, for each subject, on sections from the atlas of Paxinos and Watson (1986). Lesioned areas were quantified using an IBM Sigmascan computer program and were compared to the total area of the structure in that section to derive a percentage of the structure included in the lesion.

Data Analysis

The Wilcoxon matched-pairs signed-ranks test was applied to the data, including comparisons between the animals' performances on the first 10 and last 10 trials both pre- and postoperatively (a measure of task [re]acquisition), and between the last 10 trials prelesion and the first 10 trials postlesion (a measure of lesion effect). Comparisons between lesioned and control animals were made using the Mann-Whitney *U* test.

RESULTS

Histology

Six of the 7 lesioned animals received large and complete lesions of the MD nucleus. Lesion size averaged 93% in the left MD nucleus and 88% in the right MD nucleus. Lesions were more complete in the anterior portion and body of the MD nucleus: the extreme posterior portion was less completely damaged (35.6%). For 1 subject, MD lesion was much more restricted: at its greatest extent, only 60% of the left MD and 40% of the right MD was damaged. It is interesting to note that this subject was considerably less impaired behaviorally than the other subjects, and improved appreciably over trials. In general, the greater the damage to MD, especially to the anterior portion of the nucleus, the greater the behavioral impairment.

Hippocampal damage was inflicted in 4 animals, but this was minimal and confined to the midline. The behavioral profile of these animals did not differ from those of animals with lesions more restricted to the MD nucleus. Thalamic structures other than MD variously affected by the lesion included the paraventricular, parafascicular, and paratenial nuclei, some of the anterior thalamic group (parts of the anteromedial, anteroventral, and anterodorsal nuclei), the centromedian complex, parts of the lateral nuclei, and the habenular complex. Various portions of the above were included in the lesions of different animals. The stria medullaris and habenula were spared completely in 2 of the subjects. Figure 1 portrays a representative lesion, at several levels throughout the extent of MD.

Behavior

Prior to surgery, the animals in both groups exhibited a reduction in total errors over trial ($W = 0$, $p < .02$) and learned to make significantly more correct responses before committing an error ($W = 0$, $p < .02$).

Animals given lesions of the MD nucleus performed poorly upon reexposure to the maze. Compared to preoperative performance, animals with MD lesions made

significantly more errors ($W = 0$, $p < .02$), and made these errors sooner ($W = 0$, $p < .02$). Control subjects continued to perform well. Over the course of the 30 trials, subjects with MD lesions showed no improvement on either measure. Furthermore, control animals performed significantly better on the radial maze task than did animals with MD lesions postoperatively ($U = 0$, $p < .02$ for both total errors and number of correct choices before an error).

The results are displayed graphically in Figure 2 in terms of choice accuracy. Choice accuracy was measured by determining the observed probability of a correct response occurring on each of Choices 2–8 for each subject, over blocks of 10 trials. This observed probability was corrected for the chance probability of a correct response according to the procedure of Olton and Samuelson (1976):

$$\frac{p(\text{correct})_{\text{observed}} - p(\text{correct})_{\text{expected}}}{100 - p(\text{correct})_{\text{expected}}} \times 100,$$

where $p(\text{correct})_{\text{expected}}$ refers to the number of arms not yet chosen in that sequence divided by the total number of arms (eight) and multiplied by 100. This formula yields a number ranging from 100 (for correct performance on that choice on all trials) through 0 (chance performance) to -100 (for incorrect performance on that choice on all trials). Thus, accuracy scores around 0 indicate chance-level performance, whereas negative accuracy scores would indicate performance that is worse than would be expected by chance.

Given this index, it is obvious that the postoperative choice accuracy of animals given MD lesions decreased dramatically to near-chance levels for Choices 4–8, and

Figure 2. Choice accuracy in a cued environment, before and after lesion of the thalamic mediodorsal nucleus. The probability of a correct choice being made on each of Choices 2–8 is presented as a percentage (transformed to correct for chance; see text) of the number of opportunities for a correct response (10 trials before surgery and 10 trials after surgery). An immediate decrease in choice accuracy occurred in subjects given MD lesions.

was significantly worse than the accuracy level of intact animals over Choices 3-8 ($ps < .02$). In contrast, the preoperative performance of the two groups was identical.

As we had found previously in the visually deprived environment, response patterning typified the postoperative performance of rats given MD lesions. Four of the 7 animals developed striking patterns that involved choosing an arm at one particular angle with respect to the one just exited on more than 50% of the choices made. One animal, in particular, used an adjacent-arm strategy (45° angles between choices) on 65% of postoperative choices (compared to a 3.4% choice of arms at this angle on preoperative trials). The other 3 animals exhibited more moderate patterning.

DISCUSSION

Lesion of the mediodorsal thalamic nucleus severely impaired retention of a preoperatively learned radial maze habit, and prevented reacquisition of this task, at least within the 30 trials administered. Thus, abundant visual cues in the testing environment did not protect against a deleterious effect of MD lesion on radial maze performance. This point is important to emphasize, for it implies that the MD lesion-induced impairment of radial maze performance found previously (Stokes & Best, 1988) does not rely on a deprived visual environment to be expressed.

In contrast to these results are those of Kolb et al. (1982), who trained animals postoperatively on a version of the radial maze task in which only four out of the eight arms were baited. In that study, MD-lesioned animals performed comparably to controls. The present results reaffirm that a difference in maze environment (visually cued vs. noncued) could not have been solely responsible for the difference in experimental outcome between the Kolb et al. (1982) and Stokes and Best (1988) studies.

Potentially, differences in lesion size or placement could provide a trivial explanation of the outcome variation between those studies. Indubitably, complete lesion of MD (at least 80%) is necessary to obtain an effect. Some degree of recovery may be possible when lesion of MD is incomplete, as seen in 1 subject in the present experiment. A longer surgery-testing interval may also contribute to enhanced recovery; however, this possibility is less likely given the maintained deficit in animals tested up to 3 months after MD lesion in the Stokes and Best (1988) study. It is unknown whether behavioral recovery may depend on some interaction between a prolonged recovery interval and a visually enriched testing environment.

No resolution of these differences is possible at this juncture. Obviously, an attempt to replicate the procedure of Kolb et al. (1982) must be made before any conclusions can be drawn. Perhaps a reduced memory load (four locations as opposed to eight locations) may improve performance. Preliminary observations in this laboratory indicate, however, that this explanation may not be sufficient.

As we found previously (Stokes & Best, 1988), patterned responding guided postlesion arm choice on the maze. This occurred despite extensive experience on the maze without the use of such patterning, and despite the existence of abundant extramaze visual cues, which should have rendered each arm distinct, and of intramaze olfactory cues from each animal's own odor trail. These results imply that MD-lesioned animals cannot make use of preoperatively established information or strategies to solve the maze task, nor can they use available environmental information, including visual and olfactory cues, to establish new, effective solutions. Animals with lesions of MD are deficient at olfactory discrimination tasks (e.g., Eichenbaum, Shedlack, & Eckmann, 1980), as well as at tests of visual discrimination (Means, Huntley, Anderson, & Harrell, 1973; Tigner, 1974), and impairments in either modality may compromise radial maze performance. At this point, no mechanism for the emergence of response patterning can be postulated; a general lesion-induced reduction in available strategies may merely result in the emergence of less flexible and less adaptive modes of responding. Interestingly, however, evidence suggests that the expression of response patterning in animals given MD lesions may be modified to some extent by changes in experimental parameters (unpublished observations).

Impairment of radial maze performance in MD-lesioned animals supports the contention that a diencephalic memory system may exist in parallel with the classic hippocampal-temporal lobe system studied so intensively. Clinical data suggest that this diencephalic system, which includes the MD nucleus, may mediate a general function with respect to information encoding and attention mechanisms (e.g., Winocur, 1985). Our data provide support for this interpretation: the nonspecific impairment of retention (present study) and acquisition (Stokes, 1988), and the tendency toward stereotyped response patterning, as well as data from other studies underway in this laboratory, all indicate that cue-utilization mechanisms may be impaired in animals with MD lesions, in such a manner that memory deficits emerge as secondary phenomena.

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