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Striatal Lesions Interfere with Acquisition of a Complex Maze Task in Rats

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Abstract

The 14-unit T-maze had proven to be a valuable tool for investigating age-associated memory impairment (AAMI). While another task widely used to evaluate AAMI, the water maze, is primarily used to evaluate allocentric hippocampal-dependent spatial memory, the 14-unit T-maze can assess egocentric procedural memory. Although several brain structures, e.g. hippocampus, parietal cortex, have been implicated in acquisition and retention performance in the 14-unit T-maze, there has been no evaluation of the involvement of the striatum, a brain region implicated in procedural learning and memory. The current study revealed that excitotoxic lesions of the medial or lateral striatum significantly impaired acquisition, as measured by errors and latency, on this task without disruption of motor function. These results indicate that the 14-unit T-maze most likely requires a large egocentric procedural learning component, and previously observed AAMI may involve age-related dysfunction of the striatum.

Keywords

striatum; maze; learning; excitotoxic lesion; rats

1. Introduction

The 14-unit T-maze has proven to be a valuable tool for investigating age-associated memory impairment (AAMI) in rodents. Although not as widely used as the water maze, this task reliably detects AAMI in a variety of rodent species (1–4). Performance in this maze requires the rodent to learn a series of left and right turns to reach the goal box and in the process avoid the onset of a mild foot shock and thus may tax other neural systems not thought to be required for water maze performance. The water maze has been described as a hippocampal-dependent allocentric (externally-centered or map-based) spatial task because optimal performance

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requires localization of a hidden escape platform defined by the relations among extra-maze distal cues. The 14-unit T-maze is also sensitive to manipulations that impact hippocampal function (5). However, the sequence of turning responses may require an egocentric (body-centered) component that is sensitive to striatal processing independent of spatial cue requirements. Indeed, studies indicate intact vision is not necessary for accurate performance in rats (6), and rats run in the dark perform just as well, if not better, than rats run with illumination, (1). Therefore, it appears successful performance in the 14-unit T-maze does not require the use of visual spatial cues, suggesting a reliance on proprioceptive egocentric cues that serve to guide learning.

Although there is a clear distinction between hippocampally-dependent allocentric learning in the water maze and striatal-dependent egocentric learning in other traditional mazes, evidence suggests that both processes may contribute to performance in different maze tasks. For example, striatal lesions produce profound deficits in the standard place task (7,8) and other variations of the water maze (9–11). These findings are consistent with the idea that movement through the water maze environment is critical to forming a cognitive map (12), just as the 14-unit T-maze may involve egocentric spatial learning requiring the organism to use proprioceptive information based on their own movement to navigate through an environment (13). This defined sequence of movements is hypothesized to be based on procedural learning (7,14), which has been linked to a neural memory system that includes the striatum (9,15). Lesions of the dorsal striatum interfere with the ability of rats to utilize egocentric responses (16–19), and infusion of lidocaine into this area interferes with egocentric learning (11).

Lesion studies have been conducted to assess which brain areas may be critical for performance in the 14-unit T-maze. Pretraining and postraining electrolytic fimbria-fornix lesions impaired performance in young rats (5,20), and pretraining electrolytic lesions of the medial septal region disrupt acquisition (21). However, postraining lesions of the parietal cortex did not impair retention unless the lesion extended into the dorsal or lateral hippocampus (22), and lesions of the nucleus basalis magnocellularis did not impair acquisition in this task (23). These findings suggest that specific brain regions are involved in the acquisition and retention of performance in the 14-unit T-maze.

Although the dorsal striatum of the rat appears homogeneous morphologically, neuroanatomical and histochemical studies reveal much heterogeneity between subregions and neurochemical compartments (24–27). Further, behavioral studies have demonstrated functional heterogeneity between subregions (28). For example, lesions of the dorsomedial and dorsolateral subregions of the striatum produce different effects on water maze performance guided by allocentric versus cue-based egocentric spatial information (29,30). The findings suggest that the dorsomedial striatum may interact cooperatively with the hippocampal system during allocentric spatial performance; whereas, the dorsolateral striatum may mediate simple stimulus-response habit formation and egocentric responding.

In the present study we hypothesized that lesions of the striatum would disrupt acquisition in the 14-unit T-maze. In addition, we were also interested in evaluating the potential differential contributions of the medial and lateral striatal subregions on performance in the 14-unit T-maze, as has been observed in the water maze (7,29). If the task primarily involves egocentric procedural learning, then pretraining lesions of the dorsolateral striatum may produce a severe deficit in acquisition with lesions of the dorsomedial subregion having little or no effect. In contrast, if allocentric spatial learning is important and/or if the dorsomedial subregion also contributes to egocentric performance, then lesions of this subregion may also disrupt performance.

2. Materials and methods

2.1. Subjects

A total of twenty-five 3-month-old naïve, virgin male Fischer-344 rats weighing ~250–300 g were shipped to the Gerontology Research Center from the National Institute on Aging colony at Harlan-Sprague Dawley (Indianapolis, IN). The rats were housed 3/cage, in large suspended plastic cages in a vivarium maintained at 21°C and on a 12:12 h light:dark photocycle (lights on 07:00 h EST). Water and food (NIH-07) was provided ad libitum. All rats were acclimatized to the vivarium for at least 1 week prior to the surgery. All procedures described below were approved by the National Institute on Aging Institutional Animal Care and Use Committee and were carried out in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health.

2.2. Surgery

Rats were anesthetized using the inhalation anesthetic, isoflurane (2 ½–5%) mixed with oxygen. The scalp was shaved and cleaned with Betadine followed by a 70% alcohol solution before being placed into a small animal stereotaxic instrument (Stoelting). A local anesthetic (1% xylocaine with epinephrine) was administered immediately prior to incising and retracting the scalp to expose the skull surface. Stereotaxic coordinates were determined using the atlas of Paxinos & Watson (31) based on a flat skull position with bregma as the reference point. A handheld Dremel tool was used to drill two holes (~1 mm diameter) through the skull surface. Lesions were directed at the following stereotaxic coordinates relative to the bregma: dorsomedial striatum (+0.7 mm anterior-posterior, $\pm$ 2.4 mm medial-lateral, –5.7 mm dorsal-ventral); dorsolateral striatum (+0.7 mm anterior-posterior, $\pm$ 3.4 mm medial-lateral, –5.7 mm dorsal-ventral). The microsyringe needle was then lowered to the target coordinates and left in place for 1 min. Kainic acid (K0250: Sigma-Aldrich, St. Louis, MO, USA) was infused 0.5 µg/side in a volume of 0.25 µl/side at a rate of 0.125 µl/min. At the completion of the infusion, the syringe was left in place for 2 min to allow for diffusion of the kainic acid. For the control group the surgery was the same except the injection needle was not lowered into the brain and nothing was infused. At the completion of surgery, the wound was cleaned and closed with surgical clips. A topical antibiotic (Neosporin) was applied to the wound, and animals were allowed to recover from the anesthetic in a plastic holding cage placed on a warming pad maintained at 32° C. Animals were administered s.c. injections of 0.05 mg/kg buprenorphine and monitored daily during the 7–10 d recovery from the anesthetic and surgery.

2.3. Behavioral apparatus and procedure

As described in detail previously (see 32,33,34), a straight runway 2 m long and constructed of clear plastic was used for pretraining in one-way active avoidance. The runway had a grid floor comprised of stainless steel bars that were wired to receive scrambled shock (alternating current) from a Coulbourn Instruments (E13-08) grid floor shocker. Black plastic boxes with a guillotine door at the front and a movable rear wall served interchangeably as start and goal boxes. A hand-held switch was wired to a clock that automatically initiated a mild foot shock (0.8 mA; maximum duration 120 s, inter-shock interval 100 s) once 10 s had elapsed.

Prior to pretraining in the straight runway, the rats were moved to the testing room in their home cages and allowed to acclimatize for at least 30 min. A rat was then removed from the home cage, placed into one of the black boxes which was moved into the start area over the grid floor. The guillotine door was opened, and the rat was pushed gently forward onto the grid floor using the movable back wall. Rats had 10 s to avoid scrambled foot shock by moving down the straight runway and entering a black box at the opposite end. After 10 s, the foot shock continued until either the rat entered the goal box, or 120 s had elapsed. The guillotine door was lowered after the rat entered the goal box. A 90 s intertrial interval intervened between

trials. Criterion for successful completion of straight runway pretraining was 13 out of 15 successful avoidances, in 10 s or less per trial (maximum 30 trials). All rats that successfully met the criterion were assigned to one of the drug groups described above and trained in the 14-unit T-maze.

2.3.2. Complex maze training—More extensive details on the layout, construction and the behavioral protocol can be found in Spangler et al. (see 32,33,34). The maze was separated into five sections by guillotine doors that prevented animals from backtracking into previous sections of the maze. Non-functional guillotine doors were placed at the entry to each cul-de-sac of the maze to prevent the actual doors from being used as cues to the correct pathway. A switchbox triggered a clock which, when timed out, initiated a second clock to record the duration of shock (maximum of 5 shocks per trial). Infrared photocells were positioned throughout the maze and were wired in series to a microprocessor that recorded movement through the maze, time elapsed from start to goal, and time between photocell interruptions.

Data collected from the photocells were analyzed by the microprocessor which calculated the number of errors (defined as any entrance into a maze section leading to a cul-de-sac) and runtime for each section of the maze. Data from the microprocessor were transferred to a personal computer for more detailed analysis as well as storage of raw data. The maze was surrounded by gray walls to reduce extra maze visual cues. Speakers were located under the maze and provided music to mask auditory cues. The maze could be hoisted by motor-driven pulleys in order to clean the grid floor and reduce the presence of odor cues.

Consistent with pretraining, rats were brought to the testing room in the home cage and allowed to acclimatize for at least 30 min before drug administration and acquisition training in the 14-unit T-maze. The rat was then taken from its home cage and placed into a black start box which was positioned at the start location of the maze. The rat was pushed gently into the first section of the maze, and the guillotine door was closed. A manual switch initiated a clock that controlled the shock contingency. The rat then had 10 s to pass through the first guillotine door and enter the next section. Failure to meet this criterion resulted in a scrambled foot shock (0.8 mA) that was terminated when the rat passed through the door or a maximum of 300 s elapsed, resulting in the termination of the trial (testing was discontinued after two terminated trials). The shock contingency was reset after the rat passed through each guillotine door, completing each of the five maze sections and entering the goal box. A 90 s intertrial interval was used, during which time the box was placed in a holding area while the grid floor was cleaned with a 95% solution of ethanol solution. Each rat received a total of 15 massed trials (subsequently collapsed into five blocks of three trials for purposes of statistical analysis and data presentation).

2.4. Histology

At the conclusion of behavioral testing, rats were given an overdose of sodium pentobarbital and perfused intracardially with 0.9% saline followed by 10% formalin. The brains were removed and immersed in a 30% sucrose-formalin solution for at least 3 days. Coronal sections (50 μ m) were cut through the striatum. The sections were stained with cresyl violet and were examined under a light microscope for lesion location and extent. Examination of the lesions revealed small lesions located within the striatum (see Figure 2D).

2.5. Data analysis

Maze errors and run time were analyzed with a 3 (Group) X 5 (Trial Block) mixed analysis of variance (ANOVA) with Trial Block as the within-subjects factor. Lower order ANOVA and post hoc tests with Bonferroni correction were used when appropriate.

3. Results

3.1 Lesions

Examination of the lesions revealed small lesions located within the striatum (see Figure 2D). Compared to previous studies evaluating lateral versus medial striatal lesions (7, 29), these lesions were located more ventral, and the lesions also encompassed a much smaller area of the striatum.

3.2 Errors

As observed in Figure 2A, the medial and lateral lesion groups committed substantially more errors than the control group and did not show much improvement at any point during acquisition. The ANOVA for errors indicated main effects for Group ($F_{(2,22)} = 45.10$, $p < 0.001$) and Trial Block ($F_{(4,88)} = 23.08$, $p < 0.001$), as well as a Group X Trial Block interaction ($F_{(8,88)} = 23.08$, $p < 0.001$). Post hoc tests revealed that except for Trial Block 1, the medial and lateral lesion groups made significantly more errors than the control group at Trial Blocks 2–5 ($p < 0.01$), and the two lesions groups did not differ from each other at any of the Trial Blocks ($P > 0.05$). The lack of a difference at Trial Block 1 indicates that the lesions most likely did not produce non-specific effects on shock sensitivity or motor function as the lesion groups were similar to the control group prior to any significant learning in the control group.

3.3 Run time

Both lesion groups had longer latencies to complete trials in the maze throughout acquisition (see Figure 2B). The ANOVA for run time showed a significant main effect for both Group ($F_{(2,22)} = 13.79$, $p < 0.001$) and Trial Block ($F_{(4,88)} = 29.854$, $p < 0.001$), and a Group X Trial Block interaction ($F_{(8,88)} = 3.915$, $p < 0.001$). Post hoc tests indicated similar run times for all groups at Trial Block 1 ($p > 0.05$), indicating no baseline differences resulting from motor or sensory deficiencies. At Trial Block 2 only the lateral lesion group had a slower run time ($p < 0.01$) than the control group, while the medial group was not different ($p > 0.05$). For Trial Blocks 3–5 both lesion groups performed significantly worse than the control group ($ps < 0.05$). The lesion groups were not significantly different from each other at any of the Trial Blocks ($ps > 0.05$).

3.4 Straight run

The data from pretraining in the straight run was analyzed to evaluate potential non-specific effects on motor performance or shock sensitivity. If the lesions had an impact on either of these measures, then the number of trials to reach criterion would be increased, indicating a deficit in mobility or motivation, compared to the control group. A one-way ANOVA for Group ($F_{(2,22)} = 0.630$, $p > 0.05$) indicated no significant differences in the number of trials required to reach the criterion for completion of pretraining in the straight run (see Figure 2C).

4. Discussion

Lesions of the medial or lateral striatum interfered with the ability of rats to acquire a complex maze task without apparent impairments in non-specific motor functions or shock sensitivity. Learning as measured by errors and run time, the two primary measures of learning in this maze, did not substantially improve during acquisition for rats in either lesion group. In fact their performance near the end of training exhibited only modest improvement over performance during initial trials. Based on evidence implicating the striatum in egocentric forms of procedural learning (16–19), this finding suggests successful navigation of the 14-unit T-maze may be a procedural learning component, and there appears to be no difference between

the contributions of the medial or lateral striatum for this particular task, possibly consistent with evidence of both medial (35) and lateral (10) involvement in egocentric responding.

There is evidence for differences in the contributions of the dorsolateral and dorsomedial striatum on learning and memory tasks (7,8,29,36). More specifically, in the water maze a dorsomedial lesion impaired the acquisition of both place and cue tasks while a dorsolateral lesion had no effect (29). However, the cue impairment by dorsomedial lesions may have resulted from increased thigmotaxis, not necessarily a result of impaired learning. Evaluation of NMDA lesions within subregions of the striatum in the T-maze indicated only lesions of the posterior dorsomedial striatum, not lesions of the dorsolateral and anterior dorsomedial striatum, interfered with spatially guided behavior (37). Therefore, it appears that subregions in the striatum possess heterogeneous functions in regards to spatial learning tasks. Based on the current results, it appears that for at least the 14-unit T-maze, this heterogeneity of function may not be preserved. However, the lesions in the current study were located more towards the central portion of the striatum in the dorsal-ventral plane compared to previous studies (29,30), so the current results may not indicate the lack of a true medial versus lateral distinction in this task. Another possibility is that a simple medial-lateral distinction in the striatum is inappropriate for assigning functionality. Instead, the important difference may be between the anterior/dorsal/lateral and posterior/ventral/medial portions of the striatum (38). In this case, the lesions in the current study were not located appropriately to elucidate these functional distinctions within the striatum for the 14-unit T-maze. In addition, it is certainly possible there was a difference that was not identifiable based on the dependent measures of latency and errors. Although the mean number of errors committed, and latencies of the two lesion groups, were not different, it is possible the nature of the errors made by each group were different. For example, one group may have made more perseverative errors. Given the current set-up of the maze, this could not be evaluated further.

The striatum is not the only neural structure contributing to learning and memory in the 14-unit T-Maze. Lesions of the fimbria/fornix (5), medial septal region (21) and hippocampus (39) impair performance on this task. However, compared to the previous studies, striatal lesions appear to induce the greatest degree of impairment of any structure examined so far, e.g., in the Duffy et al. (39) study, hippocampal lesions resulted in an average of approximately 5–6 errors during the final trial block, indicating significant acquisition, while in the current study the mean error level in the lesions groups was close to 18 errors in the final trial block, indicating an almost complete absence of acquisition. It would be interesting to observe what occurs if additional training session and trials (15 trials in one session) were administered. This overtraining may have allowed the potential contribution of other neural structures, e.g., the hippocampus, to support acquisition and improve performance in the 14-unit T-maze.

Although the current results indicate the striatum contributes to acquisition, potentially dependent on egocentric processing, in the 14-unit T-maze, it is most likely not completely independent from other forms of navigation. Evidence from studies evaluating path integration, which requires the use of internal cues for successful navigation instead of integrating allocentric spatial cues, indicates the hippocampus also contributes to some aspects of egocentric processing (40,41), although the exact neural structure has not been adequately identified. As a result, it is unlikely that a single neural structure is solely responsible for processing information in a specific task, and while one structure may be primarily involved, other structures may offer some contribution (9). Instead of viewing neural structures as isolated islands in reference to cognitive processing, it is probably more realistic to consider that processing of information necessary for various types of spatial learning and memory tasks along a continuum (e.g., an egocentric-allocentric spatial reference frame). While the striatum appears to play a large role in processing the primarily egocentric spatial requirements for learning the 14-unit T-maze, other structures such as the hippocampus probably still play a

role. On the other hand, the place task in the water maze appears to be heavily dependent on hippocampal function, but certain aspects of performance may require an egocentric reference within a map-based coordinate system that may be under the control of striatal function. For more detailed discussions on the overlap and distinctions between subregions of the striatum, and between the striatum and hippocampus, please see Yin and Knowlton (42) and Johnson et al. (43).

Most learning and memory tasks include procedural components in addition to specific information (spatial or other) that is required for accurate performance. One of us (BDD) has noted in several previous water maze studies that medial lesions do not prevent animals from acquiring allocentric spatial information (7,29,30). Animals with medial caudate lesions display thigmotaxis during place acquisition that is not associated with a prolonged period of anxiety (29). Despite this impairment, which is reduced by alternating visible platform trials (Devan & White, 1999), the animals show evidence of place knowledge on probe tests following acquisition (7) and can acquire an efficient place response when visible trials are included in the acquisition phase (30). We have previously interpreted this effect as a procedural learning impairment (a deficit in initiating a place response or inhibiting wall-based thigmotaxis). Therefore, for medial lesions there is evidence of a procedural learning impairment with preserved allocentric information. On the other hand, animals with lateral lesions show weaker stimulus-response (S-R) behavior when navigating to a visible platform during a place-cue competition test (9,30). S-R behavior is considered to be a specific instance of procedural learning (habit formation) according to the declarative-procedural dichotomy of Squire (44). Therefore, what is in evidence from past studies is that both lesions disrupt procedural learning. The 14-unit T-maze, like other learning tasks, includes procedural aspects (forward movement, turning at choice points, retracing paths when encountering a blocked alley, etc.) in addition to specific egocentric spatial information (sequence of left/right responses). Based on past studies, suggesting that medial and lateral striatal lesions impair egocentric tasks and procedural components of allocentric tasks (18,19,35), the lack of difference between medial/lateral lesions in the present study is consistent with a procedural learning deficit interpretation in both cases.

The striatum, in addition to other brain areas, may be linked to the AAMI observed in previous studies (1–4), and many of these areas have been shown to be vulnerable to the neurodegenerative diseases of aging. Data from rodent and human studies indicate the striatum undergoes structural and functional changes during aging (45–48), and these alterations have been associated with learning and memory deficits. Given the evidence for AAMI in aged rodents evaluated in the 14-unit T-maze (1–4), the known age-related changes in striatal function (45–48), and the results from the current study indicating a role for the striatum in 14-unit T-maze acquisition, it appears reasonable to hypothesize that age-related changes in the striatum may contribute to procedural learning associated with AAMI. Therefore, the development and evaluation of compounds capable of attenuating or reversing these alterations offers a potential avenue for ameliorating certain aspects of AAMI.

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Fig. 1. Schematic diagram showing the configuration of the 14-unit T-maze. Arrows indicate the correct pathway. Errors are defined as any deviation from the correct pathway with more than half of the rat's body within the incorrect alley. S = start box, G = goal box, — = guillotine door, - - - = false guillotine door.

Fig. 2. Effects of lesions of the lateral and medial striatum on A) mean number of errors (± 1 s.e.m.); B) mean latency to complete the maze (± 1 sem); C) mean number of trials to attain criterion during straight run pre-training. The graph shows data plotted in blocks of three trials, except for panel C which simply represents overall group means. Symbols: * indicates $p < 0.05$ for the comparison between the control and lesion groups. D) Indicates minimum = ■; and maximum = ■ lesion extent for both the medial and lateral lesion groups.