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Research report

Striatal lesions interfere with acquisition of a complex maze task in rats

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ABSTRACT

The 14-unit T-maze has 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 is requires a large egocentric procedural learning component, and previously observed AAMI may involve age-related dysfunction of the striatum.

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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 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 hippocampal-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

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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 posttraining electrolytic fimbria–fornix lesions impaired performance in young rats [5,20], and pretraining electrolytic lesions of the medial septal region disrupt acquisition [21]. However, posttraining 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 ($2^{1/2}$–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 and 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, ±2.4 mm medial–lateral, −5.7 mm dorsal–ventral); dorsolateral striatum (+0.7 mm anterior–posterior, ±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 buprenorphrine and monitored daily during the 7–10 d recovery from the anesthetic and surgery.

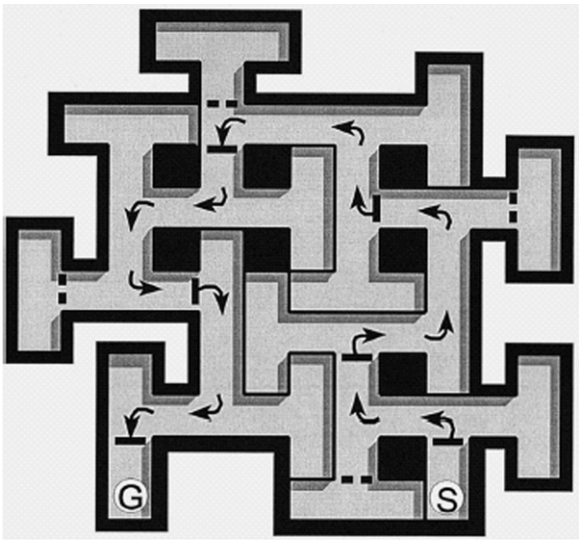

Fig. 1. Schematic diagram showing the configuration of the 14-unit T-maze. Arrows indicate the correct pathway. Errors are defined as any deviation from the correct pathway with more than half of the rat's body within the incorrect alley. S = start box, G = goal box, — = guillotine door, –·–·– = false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

2.3. Behavioral apparatus and procedure

As described in detail previously (see [32–34]), 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 handheld 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.

2.3.1. Complex maze training

More extensive details on the layout, construction and the behavioral protocol can be found (see [32–34]). The maze was separated into five sections by guillotine doors that prevented animals from backtracking into previous sections of the maze (see Fig. 1). 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