

Path Integration and Lesions Within the Head Direction Cell Circuit: Comparison Between the Roles of the Anterodorsal Thalamus and Dorsal Tegmental Nucleus

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Experiments were designed to determine whether 2 regions of the head direction cell circuit, the anterodorsal thalamic nucleus (ADN) and the dorsal tegmental nucleus (DTN), contribute to navigation. Rats were trained to perform a food-carrying task with and without blindfolds prior to receiving sham lesions or bilateral lesions of the ADN or DTN. ADN-lesioned rats were mildly impaired in both versions of the task. DTN-lesioned rats, however, were severely impaired and showed reduced heading accuracy in both task versions. These findings suggest that although both the DTN and ADN contribute to navigation based on path integration and landmarks, disruption of the head direction cell circuit at the level of the DTN has a significantly greater effect on spatial behavior than lesions of the ADN.

Keywords: head direction cell, anterodorsal nucleus of the thalamus, dorsal tegmental nucleus, path integration, rat

Knowledge of directional heading and location is an essential element of spatial navigation. Accurate spatial orientation and navigation require the use of two systems that enable the rat to estimate its location and direction in space from multiple sensory cues (Gallistel, 1990; McNaughton, Knierim, & Wilson, 1995; O'Keefe & Nadel, 1978). First, an animal can navigate using stable external stimuli, or allothetic cues, a behavior that has been referred to as landmark navigation or piloting. In the absence of familiar landmarks, cues from idiothetic, or self-movement, systems (i.e., vestibular, motor efference copy/proprioceptive, and optic flow) provide the rat with sufficient sensory information to support accurate spatial navigation. This second navigational strategy is referred to as *path integration* or *dead reckoning*. In path integration, an animal computes its position relative to a starting location by integrating cues generated by its movements between a starting position and its present location.

Two types of allocentric spatial cells have been identified in the rodent brain: place cells and head direction (HD) cells. Place cells discharge when an animal is located in a specific place in an environment. They are observed throughout all the hippocampal subfields (CA1, CA3, dentate) as well as the subicular complex

and entorhinal cortex (Cacucci, Lever, Wills, Burgess, & O'Keefe, 2004; Fyhn, Molden, Witter, Moser, & Moser, 2004; O'Keefe, 1976; Quirk, Muller, Kubie, & Ranck, 1992; Sharp & Green, 1994; Taube, 1995b; reviewed in Best, White, & Minai, 2001). The presence of place cells has provided an empirical basis for maintaining that the hippocampus plays an important role in behaviors that require a representation of the animal's location in an environment (O'Keefe and Nadel, 1978). HD cells discharge maximally whenever the animal's head is pointed in a particular direction in the azimuthal plane, independent of the animal's location and ongoing behavior (reviewed in Sharp, Blair, & Cho, 2001; Taube & Bassett, 2003). Because HD cell information projects to the entorhinal cortex (Van Groen & Wyss, 1990), the origin of major input into the hippocampus, their occurrence also supports the notion that the hippocampus plays an important role in high-level spatial cognition. HD cells were initially identified in the dorsal presubiculum (postsubiculum) (Taube, Muller, & Ranck, 1990a) and have since been reported in a number of different brain areas, particularly within the Papez circuit of the limbic system. They are most prevalent in the anterodorsal thalamic nucleus (ADN; Taube, 1995a), which, together with the anteroventral and anteromedial groups, forms the anterior thalamic nuclei. Combined lesion and recording studies have suggested that the directional signal originates in the connections between the dorsal tegmental nuclei (DTN) and the lateral mammillary nuclei (LMN; Bassett & Taube, 2001a; Blair, Cho, & Sharp, 1999; Sharp, Tinkelman, & Cho, 2001). Furthermore, the directional signal is thought to be dependent on an intact vestibular system, as neurotoxic or reversible lesions of the vestibular labyrinth abolish direction-specific firing in the ADN and postsubiculum (Stackman, Clark, & Taube, 2002; Stackman & Taube, 1997). Taken together, current theories postulate that there is a hierarchical scheme for processing directional heading information as it flows from the vestibular nuclei to the postsubiculum, making synaptic connections in the nucleus prepositus (NPH) → DTN → LMN → ADN → postsub-

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iculum. In turn, the postsubiculum sends projections to the superficial layers of the entorhinal cortex, which is the origin of the perforant pathway into the hippocampus. Once directional heading information reaches the hippocampus, it can be integrated with information about the animal's location; together, this information provides a sense of the animal's spatial orientation in the environment, which is then used for navigation.

The preferred firing direction of HD cells can be controlled by both allothetic and idiothetic cues. Rotation of a prominent visual landmark leads to an equal shift in the preferred directions of HD cells (Taube, Muller, & Ranck, 1990b). Similarly, when an animal moves from a familiar environment to a novel one, idiothetic cues are able to maintain the cell's preferred direction in the new environment (Taube & Burton, 1995) as long as the animal is able to self-locomote between the two environments (Stackman, Golob, Bassett, & Taube, 2003).

Lesion studies have implicated a few key brain areas that contribute to path integration. For example, lesions of the rat hippocampus result in severe deficits in a food-carrying task that depends upon accurate path integration (Maaswinkel, Jarrard, & Whishaw, 1999; Whishaw & Gorny, 1999; Whishaw & Maaswinkel, 1998). In addition, HD cells recorded in rats with hippocampal lesions were unable to maintain a stable preferred firing direction when rats locomoted from a familiar to a novel environment, a process where accurate path integration would be critical for maintaining an accurate sense of directional orientation relative to the familiar environment (Golob & Taube, 1999). In contrast, Alyan and McNaughton (1999) reported that hippocampal lesions did not disrupt a rat's ability to move from one location to another and then return to its original starting point in total darkness. Additional investigations have implicated the retrosplenial and parietal cortices in contributing to path integration. For example, lesions of the rat retrosplenial cortex result in both path integration and piloting deficits in a food-carrying task (Whishaw, Maaswinkel, Gonzalez, & Kolb, 2001). Studies involving lesions of the parietal cortex resulted in performance deficits on a path integration task, particularly when task difficulty increased as the outbound route became more complex (Save, Guazzelli, & Poucet, 2001; see also Parron & Save, 2004; Save & Moghaddam, 1996). In contrast, lesions of the parietal cortex or dorsal hippocampus did not impair homing in a water maze task (Save & Poucet, 2000). Alternatively, other studies that have disrupted vestibular signals through neurotoxic labyrinthectomies have demonstrated the importance of the vestibular system for accurate path integration (Stackman & Herbert, 2002; Wallace, Hines, Pellis, & Whishaw, 2002). It is noteworthy that vestibular information from the vestibular nuclei is projected to the DTN through the nucleus prepositus (Brown, Card, & Yates, 2005; Hayakawa & Zyo, 1985; Liu, Chang, & Wickern, 1984) and thus is readily capable of influencing the HD cell system. The extent to which brain areas involved in the HD cell circuit contribute to path integration is not known. The present experiments address whether the DTN and ADN, sites that correspond to relatively early and late processing of the HD signal, respectively, are critically important for accurate performance in a path integration task. Previous studies have shown that lesions of the anterior thalamus can impair accurate navigation in a number of spatial tasks requiring the use of allocentric cues, including the water maze (Warburton & Aggleton, 1999), an eight-arm radial maze (Aggleton, Hunt,

Nagle, & Neave, 1996), and a forced spatial alternation task on a T maze (Aggleton, Neave, Nagle, & Hunt, 1995; Warburton & Aggleton, 1999; Warburton, Baird, & Aggleton, 1997). Rats with anterior thalamic lesions were not impaired in an object recognition test (Aggleton et al., 1995) or in spatial tasks when egocentric cues were relied on (Aggleton et al., 1996). There is also some evidence to suggest that the water maze deficits are observed only for acquisition, as postlesion performance was not impaired when the task was acquired before surgery (Sutherland & Rodriguez, 1989). Some behavioral studies that have focused on comparing different subregions of the anterior thalamic nuclei have found that small lesions involving one or two of the subnuclei produced substantially fewer deficits than did lesions that involved all three subnuclei (Aggleton et al., 1996; Van Groen, Kadish, & Wyss, 2002). These studies relied mostly on spatial tasks that were solved with allothetic spatial information and did not address the role of ADN in path integration.

Although the DTN has been well characterized anatomically (Hayakawa & Zyo, 1985, 1990), relatively little is known about its functional role in behavior. Single-unit recording studies showed that the vast majority of DTN cells fire in relation to the animal's angular head velocity (Bassett & Taube, 2001b; Sharp, Tinkelman, & Cho, 2001). A behavioral study that lesioned the dorsal and ventral tegmental nuclei reported behavioral effects that were similar to those of midbrain raphe lesions, including increased activity in an open field test and facilitated acquisition of a two-way avoidance task (Loren, Kohler, & Guldberg, 1975). Another study that lesioned the fiber tract passing between the tegmental nuclei and the mammillary nuclei reported that the lesioned animals were impaired in a delayed alternation task (Field, Rosenstock, King, & Greene, 1978). Neither of these behavioral studies addressed the path integration abilities of these animals.

The present experiments investigated the role of the ADN and DTN in a rat's ability to perform two versions of a spatial task. The task specifically required the rat to make a choice based on its angular displacement from a goal. Accurate performance in one version most likely required path integration, whereas accurate performance in the second version could occur through either the use of visual landmarks (piloting) or path integration. Rats were trained to forage for food in an open field and return to a refuge either while blindfolded (idiothetic version) or in the presence of prominent visual landmarks (allothetic version). The rats then received lesions of the ADN or DTN and, upon recovery, were tested for performance on the same two versions of the food-carrying task.

Method

Experiment 1

Animals

Sixteen naive adult female Long-Evans rats (control = 6, lesion = 10), weighing 250 to 325 g, were housed in shoebox cages in a satellite vivarium on a 12-hr light-dark cycle.

Surgery

Rats receiving lesions of the ADN were anesthetized with sodium pentobarbital (40 mg/kg ip) and atropine sulfate (5 mg/kg). Lesions of the

ADN were made through infusion of 0.15 μL of a 100-mM solution of *N*-methyl-D-aspartate into two sites per hemisphere with a Kopf microinjection unit (David Kopf Instruments, Tujunga, CA). The stereotaxic coordinates with respect to bregma were, for anterior–posterior (AP), -1.1 and -1.5 mm; for medial–lateral (ML), ± 1.4 mm; and for dorsal–ventral (DV) from the cortical surface, -5.0 mm. The solution was infused at 0.1 $\mu\text{L}/\text{min}$, and the injection needle was left in place for 3 min before withdrawal. Control rats received sham lesions. They were anesthetized, were placed in the stereotaxic instrument, and had holes drilled above the same injection sites as the ADN-lesioned rats, except the needle was not advanced into the brain.

Food-Carrying Task

The food-carrying task was similar to the task developed by Whishaw and colleagues (e.g., Whishaw, Coles, & Bellerive, 1995; Whishaw & Maaswinkel, 1998). This task relied on the rat's proclivity to carry large food pellets to a shelter for eating rather than consume them out in the open field. Briefly, a rat was placed into a refuge that led to a large open field through a curtained doorway. Once the rat was in the field it would forage for a large food pellet located in 1 of 16 small dishes. After the food pellet was found, the rat returned to one of the eight curtained doorways, with only one doorway leading to the refuge. The field floor was wiped down with a damp cloth between each trial to eliminate previous odor cues. We also took precautions to eliminate other cues from the testing environment. Whishaw and Maaswinkel (1998) demonstrated that normal rats will use an allothetic cue-based strategy to return to the refuge when those cues are available and an idiotactic cue-based strategy when they are blindfolded (negating the use of visual cues), even when odor cues are displaced from, or put in conflict with, the correct return path. We used the same techniques to test whether lesions of the HD cell circuit would impair navigation in general or in one of the strategies selectively.

Apparatus

The food-carrying apparatus consisted of a large, gray circular (1.83-m diameter) open field with 16 symmetrically placed black food cups on the surface (see Figure 1). Each food cup could be baited with a large (750-mg) sugar pellet (Bioserv, Frenchtown, NJ). The entire field was supported by four rolling casters and was mounted on a central bearing that allowed the field to be rotated around a central platform. The central platform was slightly raised (1-cm thick, 53.3 cm in diameter) and remained stationary when the large circular field was rotated to control for odor cues during probe trials. The field was surrounded by a wall (38-cm high) containing eight uniformly distributed doorways (each ~ 13 -cm wide) that were covered by a black curtain that could be parted in the middle to allow the rat to go through. There was a refuge behind one doorway (13-cm wide, 40-cm long, 30.5-cm high) that was lined with wood-chip bedding and was completely covered with a cardboard lid once the rat was placed inside at the beginning of a trial. The other seven doorways served as false refuges and had wooden barriers behind the curtains. A video camera was located above the center of the field so that the behavior of the rats could be videotaped and analyzed further offline.

Blindfolds

To prevent the use of visual cues in performing the task, we blindfolded the rats for some trials and trained and tested them in the dark. The blindfolds were made of cloth that covered the rat's eyes and could be attached by a Velcro collar that wrapped behind the ears and around the rat's neck. The blindfold was fastened across the rat's face with an elastic chinstrap that was attached to the collar. The chinstrap was flexible to allow for retrieval and chewing of the large pellets. To adapt them to the

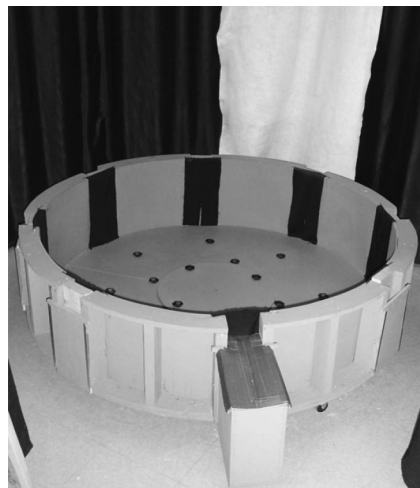


Figure 1. The test room and food-carrying apparatus. A floor-to-ceiling black curtain surrounds the maze apparatus, and a distinct white cue curtain hangs opposite the covered refuge shown in the foreground. Identical black curtains cover the doorways to the real refuge and the seven false refuges. The elevated center platform is fixed, and the outer field is mounted on a bearing with wheels and can be rotated for probe trials.

feel and use of the blindfold, prior to training we provided each rat with five daily sessions (~ 20 min) with the blindfold on in its home cage.

Feeding and Training

Before training, rats were placed on food-restricted diets (~ 15 g/d) until they attained $\sim 80\%$ of their expected free-feeding weights. They were then maintained on this diet for the entire protocol, except for a 1-week period immediately after surgery (when they were placed on an ad lib diet). At the start of training, all of the food cups were baited with pellets, and each rat was allowed to leave the refuge to forage for the pellets. Once a rat found a pellet, it typically returned to the refuge. If the rat tried to eat the pellet in the open field or search for another pellet during a return path, the behavior was discouraged by making a startling noise (e.g., shaking keys) or taking the food pellet away. Rats were allowed to retrieve four pellets per day (i.e., complete four trials). As the rats became more proficient at the task, the number of baited food cups was reduced daily until there was only one pellet available per trial. Once the rats could complete four successive retrieval trials and reliably return to the correct refuge (80% correct), they began training in the task with the blindfolds. As soon as the rats could complete four trials with the blindfolds, they were tested for accuracy in both versions of the task.

Testing

The test of accurate navigation involved 12 separate retrieval trials, spaced over 4 days, for each rat in both the visual and blindfold versions of the food-carrying task. Blindfold and visual tests were run on separate consecutive days (i.e., two days of blindfold testing followed by two days of visual testing). For each trial, the food pellet was placed pseudorandomly in one of the dishes. The placement was consistent between rats, but not between trials. The same pattern of food placement was repeated for the two versions of the task so that the visual version was not easier than the blindfold version, and vice versa. The floor of the open field was cleaned with 80% ethanol and a dry cloth after each trial. For each trial, the rat was placed in the refuge and allowed to forage for the food pellet, return to the refuge, and eat the pellet before being removed and placed in a nearby

cage. All of the test trials were videotaped and scored offline. Figure 2 shows a time line summary for pretraining, training (visual and blindfold), baseline testing, and postlesion testing procedures.

Behavior Analysis

On the basis of offline analyses of the videotapes, we divided the trials into the following classifications.

Retrieval trial. Retrieval was defined as an exit from the refuge and a return with a food pellet.

Correct trial. A correct trial was a trial in which a rat found a food pellet and returned directly to the starting doorway without stopping at any other doorway.

Error trial. An incorrect trial was one in which a rat found a food pellet, but stopped at one of the other potential exits before returning to the exit from which the excursion began. An error was scored if the rat's snout came within ~2 cm of a false doorway and if the rat broke stride from its route toward the correct doorway.

First choice. The first choice was defined as the first doorway that the rat visited after finding a food pellet.

Second choice. The second choice was defined as the second doorway that a rat visited, given that the first choice was incorrect, and a second choice could include a perseverative return to the first choice.

Initial and final heading angles. The initial heading angle was defined as the angle between the refuge and the rat's directional heading when the rat left the cup that contained the food pellet and was one body length away from the cup. The final heading angle was defined as the angle between the refuge and the rat's directional heading when the rat approached the refuge and crossed a "virtual finish line" that was 2 cm from the outside wall of the apparatus. Each angle was measured with a resolution of 5° that was either clockwise or counterclockwise from the refuge; thus, the maximum deviation was 180°.

Response times. Using a stopwatch, the experimenter recorded the time taken to find a food pellet once the rat's entire body had emerged from the refuge (search time) and the time taken to return to the refuge with the food pellet (return time). The return time encompassed the moment the rat found the correct cup until the time it returned to the refuge and usually included 1–2 s in which the rat paused at the food cup to pick up the food pellet in its mouth and turn around before embarking on its return trip.

Rotation Probe Trials

A rotation probe trial was conducted at the end of the last day of testing for each version of the task (visual vs. blindfold). On the probe trial, the rats started from the standard training refuge position. Once they reached

the pellet in the middle of the field, the outside of the field was rotated either clockwise or counterclockwise around the stationary center of the apparatus. The trial was scored correct if the rat returned to the doorway where the refuge was originally. Any other choice was scored as an error. We primarily used this probe to control for odor cues that may have been attributed to the refuge.

Histology

At the end of behavioral testing, all rats were deeply anesthetized with sodium pentobarbital (120 mg/kg ip) and perfused with 0.9% saline, followed by a 10% formalin in saline solution. Their brains were frozen, sectioned at 40 μ m, and stained with thionine for microscopic examination and verification of lesion sites. Defining areas of gliosis and the absence of neurons allowed for verification of lesion sites.

Data Analysis

We conducted comparisons of behavioral measures (i.e., errors, response times, and heading angles) on the postlesion data between control and lesioned (ADN) rats using mixed-design analyses of variance (ANOVAs; Lesion \times Condition [visual and blindfold]) for Experiment 1. Planned comparisons between visual and blindfold conditions were conducted with methods discussed by Howell (1982, p. 280 ff.). The behavioral measures for the baseline tests were scored prior to surgical lesions. On the basis of these data, the rats were divided into two groups (control and lesion), which were matched to minimize any differences between the two groups. We used a Rayleigh test (Batschelet, 1981) to determine whether error trials were random or were clustered around the correct location. For this test, the correct bin was omitted from analysis, and the number of occurrences in the remaining seven locations (that were equally spaced around a circle) was tested for randomness. The level of statistical significance was defined as .05.

Experiment 2

Methods for Experiment 2 were identical to those for Experiment 1 with the following exceptions.

Animals

Twenty rats, 10 in the control group and 10 in the lesion group, were used. Different control animals were used in Experiments 1 and 2 and were trained and tested separately.

Experimental Time Line

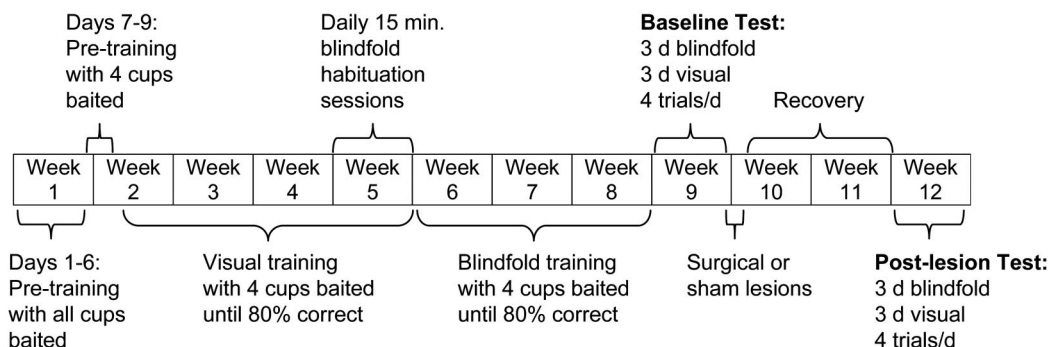


Figure 2. Time line showing experimental procedures. d = days.

Surgery

The DTN is composed of two subdivisions: dorsal and ventral. We aimed to lesion the entire DTN, including both subdivisions. We made lesions by passing 0.30 mA DC (Stolting 3500, Wood Dale, IL) through a cathodal, stainless steel insect-pin electrode (Elephant; Caroline Supply Co., Charlotte, NC) for 25 sec. The electrode was insulated except for 0.5 mm of the tip, which was scraped bare. One site was targeted per hemisphere using the following stereotaxic coordinates: for AP, -0.20 mm from interaural line; for ML, ± 0.30 mm from midline at bregma; and for DV, $+2.40$ mm from interaural line. Coordinates were based on the brain atlas by Paxinos and Watson (1998) and modified on the basis of previous histological results. Control animals were shams that had an electrode lowered to just above the DTN in each hemisphere but received no current injection.

Ascending projections from the vestibular nuclei travel through the medial longitudinal fasciculus (mlf), which passes just ventral to the DTN. Electrolytic lesions of the DTN may therefore damage these fibers, which convey angular head-velocity information and could contribute to path integration. Therefore, to aid in determining whether any effects that were to be observed in the DTN-lesioned rats were due to mlf damage, we included two additional animals that had bilateral lesions of only the mlf. The stereotaxic coordinates for these lesions using the interaural line were, for AP, $+1.1$; for ML, ± 0.4 from the midline; and for DV, $+3.0$.

Food-Carrying Task, Apparatus, Blindfolds, Feeding and Training, Testing, Behavior Analysis, and Histology

These were the same as in Experiment 1, but no rotation probe trials were conducted.

Data Analysis

Comparisons of behavioral measures (i.e., errors, response times, and heading angles) between control and DTN-lesioned rats were determined with mixed-design ANOVAs (Lesion \times Condition). Planned comparisons between visual and blindfold conditions were conducted with the methods discussed by Howell (1982, p. 280 ff.). As with Experiment 1, animals were sorted into control and lesion groups on the basis of their baseline performance scores, such that there were no statistical differences between the two groups for the baseline tests. In addition, we calculated a similar mixed-design ANOVA between ADN-lesioned, DTN-lesioned, and control animals to directly compare the magnitude of impairments between ADN- and DTN-lesioned rats. Significant ANOVAs were analyzed post hoc with Tukey's honestly significant difference tests. The level of statistical significance was defined as .05.

Results

Experiment 1

Histological Results

Figure 3 shows coronal sections of a brain with reconstruction of the smallest (black) and largest (gray) lesion extents in rats with lesions of the ADN (adapted from Paxinos & Watson, 1997). All of the ADN-lesioned rats included in the analyses ($n = 10$) sustained extensive bilateral damage to the ADN. Some rats sustained minimal damage to surrounding thalamic nuclei (i.e., anteroventral, anteromedial, laterodorsal, paracentral), although the main extent of the damage was restricted to the ADN. The stria medularis was unaffected.

Return Accuracy

All of the rats were proficient and accurate in both the visual and blindfold versions of the food-carrying task before surgery and took about 24 days to reach an 80% criterion level. Figure 4 shows that postsurgery, the ADN-lesioned group showed significantly more errors (lower percentage correct) than the control group through the main effect of lesion, $F(1,14) = 13.30$, $p < .005$. There was no significant interaction of lesion and condition, $F(1,14) = 0.09$, *ns*, and even though the ADN-lesioned rats performed a little poorer in the blindfold condition compared with the visual condition (see # in Figure 4), there was no significant main effect of condition, $F(1,14) = 3.52$, $p = .082$. Furthermore, planned comparisons revealed no significant differences for return accuracy between visual and blindfold conditions in either control or lesioned rats ($ts < 1.70$). Although the ADN-lesioned rats made more errors than the control rats, a Rayleigh test rejected the hypothesis that their errors were randomly distributed for both visual ($r = .710$, $p < .001$) and blindfold ($r = .606$, $p < .001$) conditions, and Figure 5 shows that there was a strong tendency to choose either of the adjacent doorways to the refuge.

The accuracy measures of the choice behavior were reflected in the heading angle measures, albeit in a different pattern. As shown in Figure 6, the initial heading of the ADN-lesioned rats at the beginning of their return trip deviated further from the refuge than that of the control rats, as indicated by a significant main effect of lesion, $F(1,14) = 9.52$, $p < .01$. Again, there was no significant main effect of condition, $F(1,14) = 0.55$, *ns*, or Lesion \times Condition interaction, $F(1,14) = 1.06$, *ns*. A similar pattern of results was found for the final heading measure, in which there was a significantly larger angular deviation for the ADN-lesioned group, as indicated by a significant main effect of lesion, $F(1,14) = 10.41$, $p < .01$; again, there was no significant main effect of condition, $F(1,14) = 0.53$, *ns*, or Lesion \times Condition interaction, $F(1,14) = 0.002$, *ns* (see Figure 6). Planned comparisons for both measures did not reveal any significant effects. These data suggest that the ADN-lesioned rats had some difficulty navigating accurately in both the path integration and piloting versions of the task, and although some of the deficits appeared slightly more pronounced in the path integration version than in the version in which visual landmarks could be used, this difference was not statistically significant.

Search and Return Times

The data in Table 1 show that there were no significant differences between the ADN-lesioned and control groups on either search or return times (all $F_s < 2.60$) for both the blindfold and visual versions of the task. As one would predict, the search times were longer and more variable (larger SEMs) than the return times because the rats had to search for the food pellet during the outbound trip, and the pellet was always in an unpredictable location. One question that arises from these data is why the ADN-lesioned rats had return times similar to those of the control rats in the blindfold condition if they were making more errors. Figure 5 shows that the ADN-lesioned rats did not usually miss the correct refuge by a large margin, as they usually selected doorways that were adjacent to the correct

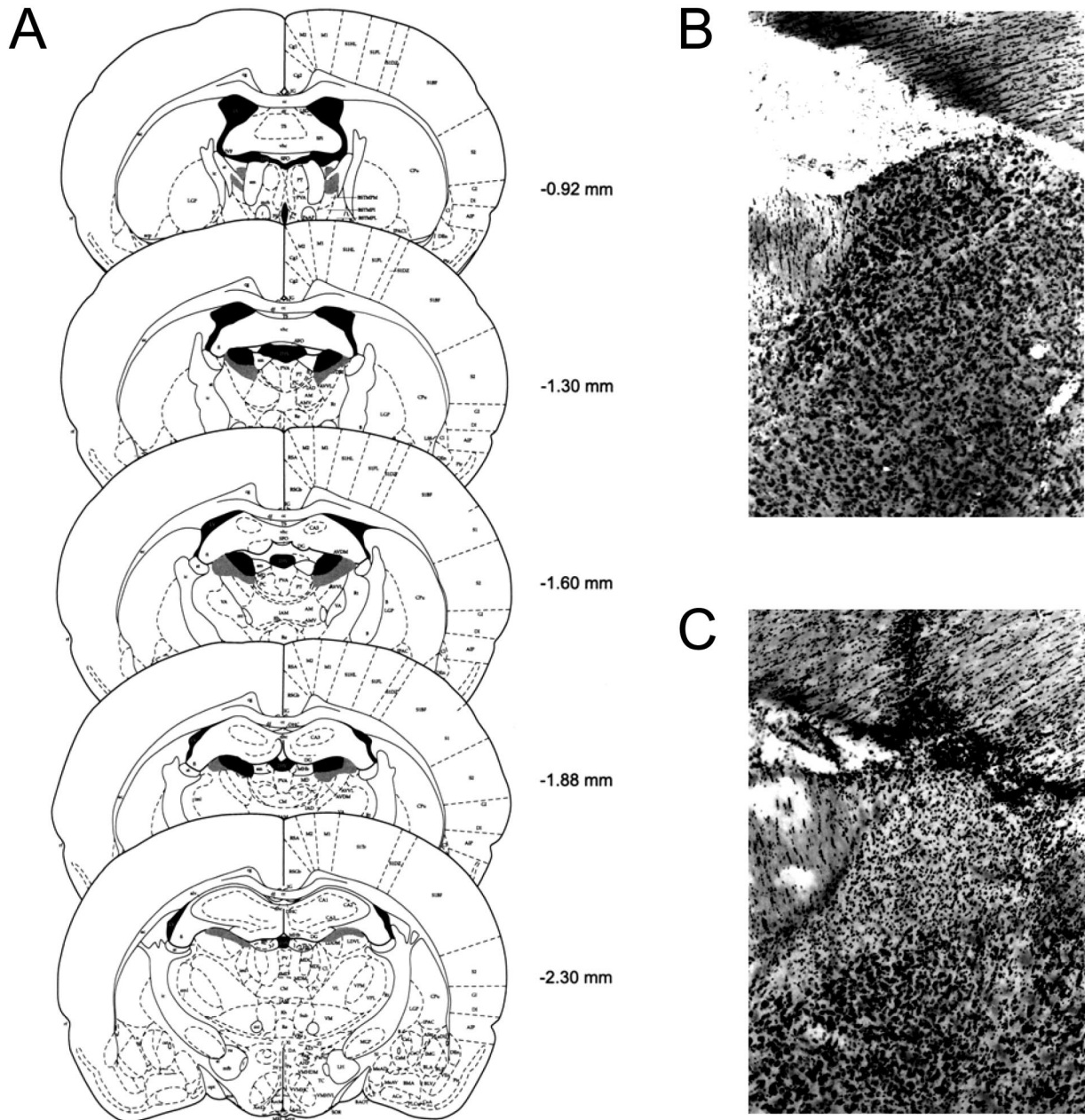


Figure 3. A: Coronal sections of the rat brain. The gray areas represent the largest extent of the lesions, and the black areas represent the smallest extent of the lesions accepted for analyses in Experiment 1. Adapted from Figures 22, 23, 25, 27, and 29 in *The Rat Brain in Stereotaxic Coordinates* (4th ed.), G. Paxinos and C. Watson, 1998, with permission from Elsevier. B: Photomicrograph showing the right anterodorsal thalamic nucleus (ADN) from a nonlesion control rat. C: Photomicrograph of a similar anterior-posterior section from an animal with an *N*-methyl-D-aspartate lesion of the ADN.

refuge and then immediately moved on to the refuge for their second choice (data not shown). Thus, the increased time it took to first select an adjacent doorway and then move on to the correct doorway was minimal and represented only a small portion of the overall return time. Therefore, the extra time it took to select two doorways was probably too short to become apparent in the total return time and may have led to the insignificant results.

Rotation Probe Trials

Using various probe trials, previous studies have shown that rats do not rely on olfactory cues in this task (e.g., Whishaw & Maaswinkel, 1998). To ensure that rats in the present study also were not using olfactory cues, we conducted a rotation probe trial with the rat blindfolded. In this trial, once the rat found the food pellet during its outbound trip, the outside

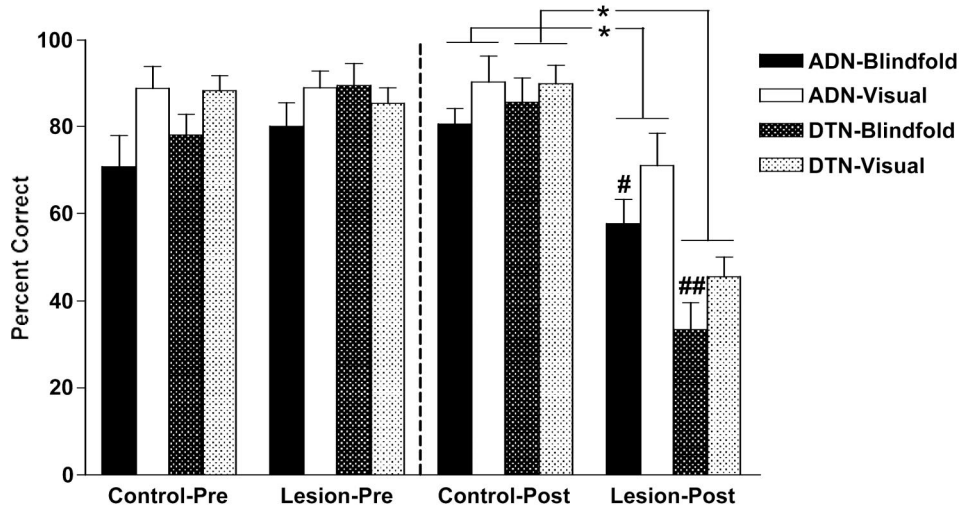


Figure 4. Mean percentage of correct test trials for prelesion (left) and postlesion (right) control, ADN-lesioned, and DTN-lesioned rats in visual and blindfold trials on the food-carrying task. Error bars represent the standard error of the mean; asterisks indicate $p < .05$. # symbols indicate small differences in performance between blindfold and visual conditions for rats with ADN (#) and DTN (##) lesions, but these differences were not significant. ADN = anterodorsal thalamic nucleus; DTN = dorsal tegmental nucleus.

portion of the platform (including the refuge) was rotated quickly while the rat was still on the stationary center portion by the food cup. If odor cues played an important role in guiding the rat's behavior, then we would expect the rat to return to the refuge in its rotated position after retrieval of a

food pellet. In contrast, if rats were not relying on odor cues and were path integrating accurately, then they should return to the doorway that was positioned in the original location of the refuge.

Because the rats would quickly return to the refuge once the food pellet was found, there was only a short time in which the

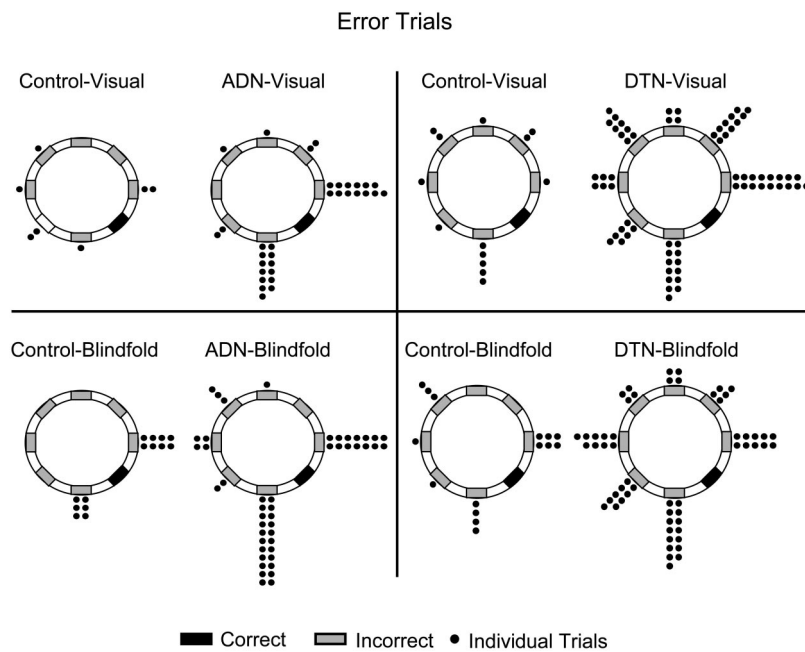


Figure 5. Circular histograms of doorway choices on error trials by control, ADN-lesioned, and DTN-lesioned rats. Correct trials are not shown. The control rats committed fewer errors than the ADN-lesioned and DTN-lesioned groups in both the visual (top) and blindfold (bottom) versions of the task. The points indicate that errors made by ADN-lesioned rats, but not DTN-lesioned rats, were typically at the doors adjacent to the correct refuge. ADN = anterodorsal thalamic nucleus; DTN = dorsal tegmental nucleus.

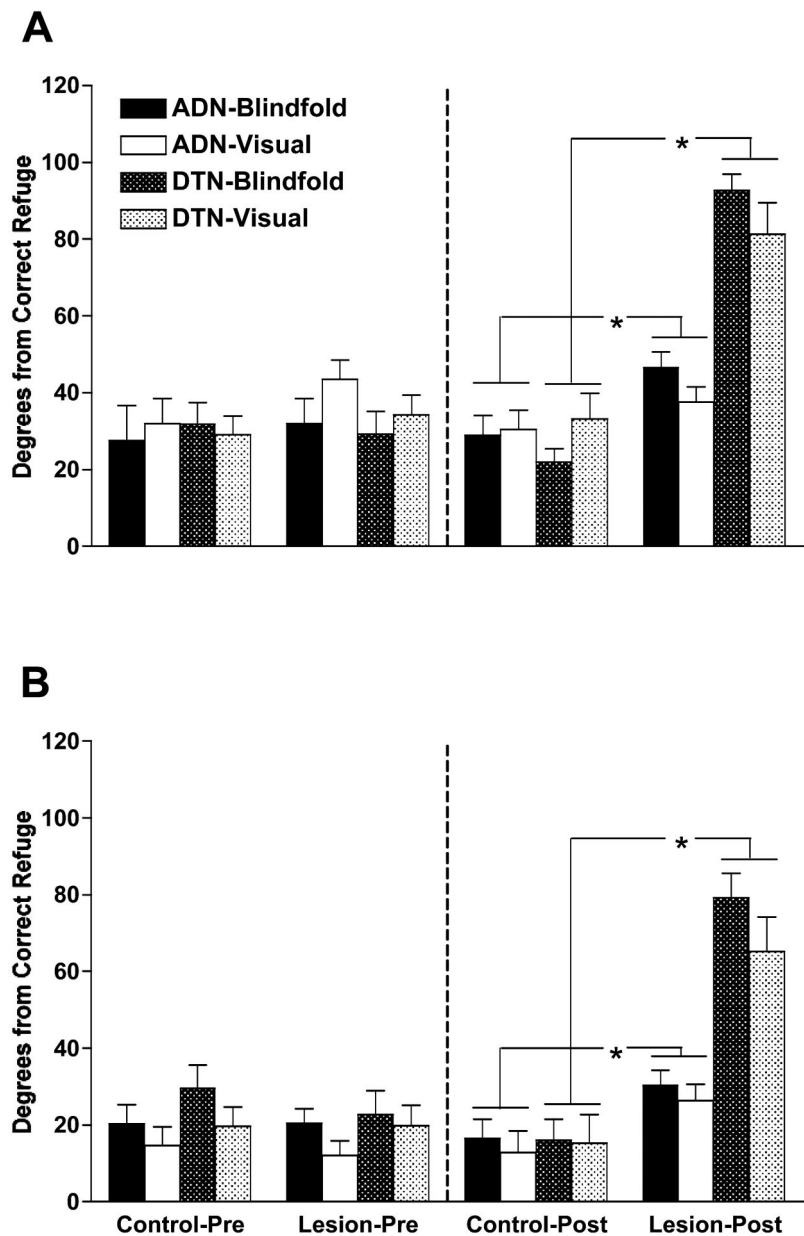


Figure 6. Mean initial (A) and final (B) heading angle test trials for prelesion (left) and postlesion (right) control, ADN-lesioned, and DTN-lesioned rats in visual and blindfold trials on the food-carrying task before (pre) and after (post) lesions of the corresponding nuclei. Error bars represent the standard error of the mean. ADN = anterodorsal thalamic nucleus; DTN = dorsal tegmental nucleus. * $p < .05$.

maze could be rotated; thus, rotations of the platform were limited to 45°. Of the rats that received probe trials (control: $n = 4$, ADN lesioned: $n = 6$), the control rats returned to the original refuge location 100% of the time, and the ADN-lesioned rats returned to the original refuge location 33% of the time (2 out of 6), with an average final heading of 32.5° from the correct doorway. Within the 67% of error trials, all of the rats crossed the virtual finish line at places adjacent to where the refuge should have been and on the side away from the

current location of the refuge. Thus, none of the lesioned rats returned to the current rotated location of the refuge, and the error rate was similar to their performance during the standard trials. These results suggest that rats in both groups were not using odor cues to navigate and reflect a similar impairment in the ADN-lesioned rats to navigate accurately. These data also show that rats with ADN lesions were not switching strategies, from path integration to reliance on odor cues, when performing the task.

Table 1
Average (\pm SEM) Search and Return Times

Condition	Search time (s)	Return time (s)
Experiment 1		
Control		
Visual	6.29 \pm 0.80	5.25 \pm 1.20
Blindfold	8.04 \pm 0.40	7.11 \pm 0.88
ADN		
Visual	7.23 \pm 0.70	5.65 \pm 1.20
Blindfold	13.5 \pm 3.82	6.71 \pm 0.71
Experiment 2		
Control		
Visual	7.29 \pm 0.79	4.49 \pm 1.25
Blindfold	10.21 \pm 0.58	4.55 \pm 0.59
DTN		
Visual	11.86 \pm 1.06*	7.91 \pm 0.67*
Blindfold	12.47 \pm 1.90	10.44 \pm 0.90*

Note. ADN = anterodorsal thalamic nucleus; DTN = dorsal tegmental nucleus.

* Significantly different from control rats at $p < .05$.

Experiment 2

Histological Results

Figure 7 shows coronal sections of a brain with a reconstruction of the smallest and largest lesion extents in rats with DTN lesions (adapted from Paxinos & Watson, 1997). Lesions were large, in general, and usually involved tissue lateral and ventral to the DTN. In one case, the lesion involved the laterodorsal tegmental nucleus unilaterally, and in another case, there was sparing in the anterior pole of the dorsal division bilaterally. The ventral division was considered the critical target, as it is the principal source of efferents to the LMN (Petrovicky, 1985). All rats included in the analysis showed complete bilateral ablation of ventral divisions of the DTN, and all but one showed complete bilateral ablation of dorsal divisions.

Lesion sites for the mlf were placed anterior to the DTN, with the intent of interrupting ascending vestibular projections without disrupting mlf fibers that terminate in the DTN. Both mlf-lesioned rats had restricted lesions of the mlf that produced no visible damage to the DTN. One case had complete bilateral ablation, and the other case had complete unilateral ablation with some sparing on the other side. In both cases, the dorsal raphe nucleus and the superior cerebellar peduncle in the region of its decussation were involved in the lesion, but neither structure sustained major damage.

Return Accuracy

One DTN-lesioned rat failed to locate and retrieve any pellets on blindfold trials. Thus, this rat was omitted from statistical analysis on blindfold trials, and only 9 control animals were used for comparison to the lesion group. For all other comparisons, $n = 10$ for both groups.

As with the ADN-lesioned rats in Experiment 1, all rats in Experiment 2 performed at least 80% correct prior to surgery. A

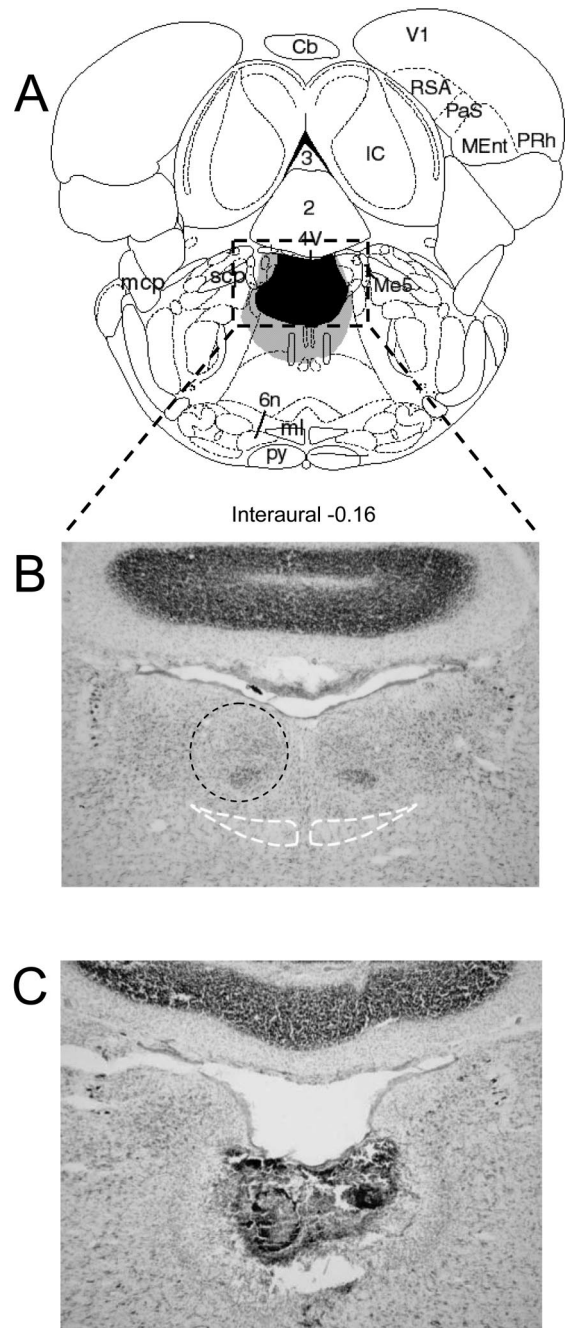


Figure 7. Histological results of dorsal tegmental nucleus (DTN) lesions. A: Figure modified from Paxinos and Watson (1998) at -0.16 mm from interaural line, showing smallest (black) and largest (gray) extents of lesions. Adapted from Figure 56 in *The Rat Brain in Stereotaxic Coordinates* (4th ed.), G. Paxinos and C. Watson, 1998, with permission from Elsevier. Dashed rectangle indicates approximate area shown in Parts B and C. B: Photomicrograph of intact DTN; dashed black circle indicates nuclei. Ventral division is visible as dark area of large cells at bottom of circled area. The medial longitudinal fasciculus is outlined in dashed white lines. C: Photomicrograph of DTN lesion.

significant main effect of lesion, $F(1,16) = 57.98, p < .001$, indicated that performance after surgery was significantly poorer for both conditions, with DTN-lesioned rats returning directly to the refuge on 45% of visual trials and on 33% of blindfold trials (see Figure 4). A significant main effect of condition, $F(1,16) = 4.499, p < .05$, indicated that both the lesion and control groups performed poorer on the blindfold version of the test compared with the visual version, but the effect was not strictly due to the lesion, as there was no significant Lesion \times Condition interaction, $F(1,16) = 0.97, ns$. Thus, although the DTN-lesioned rats performed a little poorer in the blindfold condition compared with the

visual condition (see ## in Figure 4), there was no indication that DTN lesions differentially affected path integration over landmark processes, and planned comparison tests for control and lesioned animals were not significant ($ts < 1.6$). Poor performance was consistently observed across all 3 days of postlesion testing for both visual and blindfold conditions (Figure 8A). Figure 4 shows that their performance was poorer than that of ADN-lesioned rats for both visual and blindfold conditions. Moreover, for both conditions, the doorway choices were more evenly distributed around the open field than in the error trials for ADN-lesioned rats (see Figure 5), although a Rayleigh test still rejected the hypothesis that

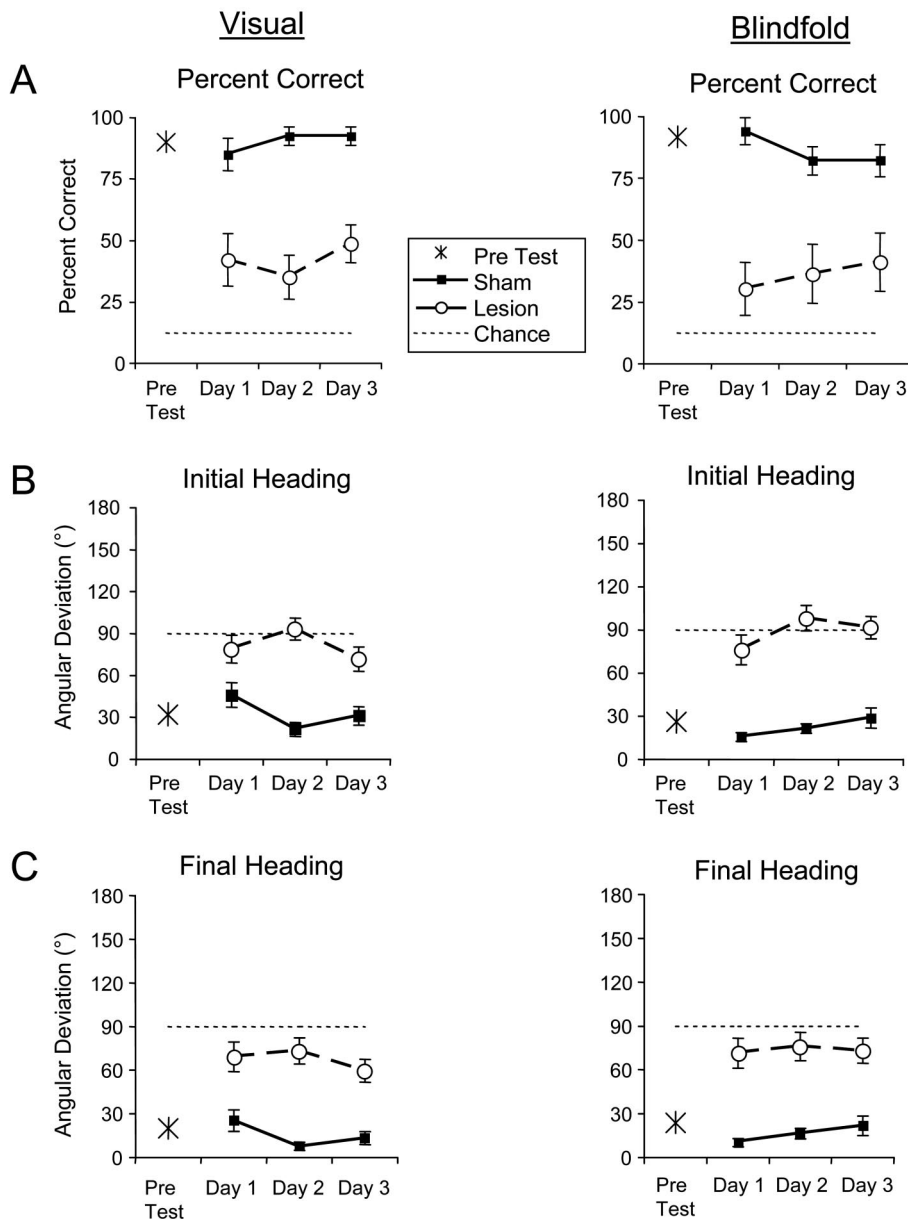


Figure 8. Postlesion performance in DTN-lesioned rats over 3 consecutive days for blindfold and visual trials. A: Percentage correct. B: Initial heading. C: Final heading. Initial and final headings are expressed as the angular deviation from the correct heading angle of 0° back to the refuge. Error bars represent standard errors of the mean. DTN = dorsal tegmental nucleus.

this pattern of errors was randomly distributed for both blindfold ($r = .300, p < .01$) and visual ($r = .232, p < .05$) trials.

Figure 6 shows that measures of heading angle, both initial (A) and final (B), were more deviated in the DTN-lesioned group compared with control rats, as indicated by a significant main effect of lesion for initial heading, $F(1,15) = 70.98, p < .001$, and final heading, $F(1,15) = 35.09, p < .001$, but the interactions for these measures indicate a slightly different pattern of behavior than for the percentage correct measure. There was a significant Lesion \times Condition interaction for the initial heading measure, $F(1,15) = 6.26, p < .05$, but no effect of condition, $F(1,15) = 0.001, ns$. The reverse was true for the final heading measure, as there was a significant main effect of condition, $F(1,15) = 4.75, p < .05$, but no Lesion \times Condition interaction, $F(1,15) = 3.77, ns$. Planned comparisons for these measures did not reveal any significant effects. The detrimental effects of the lesions were consistent across all 3 days of postlesion testing (see Figures 8B and 8C).

Search and Return Times

Unlike rats with ADN lesions, DTN-lesioned rats in the blindfold and visual conditions took longer than control rats to locate pellets and to return to the refuge afterward, as indicated by significant main effects of lesion on search time, $F(1,15) = 9.54, p < .01$, and return time, $F(1,15) = 16.37, p < .005$. There were no other main effects or interactions for these two measures ($F_s < 3.65$). DTN-lesioned rats often displayed disorganized search patterns that probably account for the differences in search time (e.g., failing to stop at food cups during search and returning repeatedly to cups they had already visited). On return trips, rats that made an error typically followed the perimeter of the maze back to the refuge, sometimes pausing at intervening incorrect doors on the way. The somewhat greater dispersal of errors and poorer heading accuracy relative to those of ADN-lesioned rats may account for the longer return times in DTN-lesioned rats, because they often simply had farther to go to return to the refuge from an incorrect choice.

mIlf Lesions

Rats with mlf lesions performed similarly to control rats in both visual and blindfold conditions. In the visual condition, rats returned to the refuge on 23 out of 23 trials (100%), and in the blindfold condition, they returned to the refuge on 18 out of 21 trials (85.7%). Errors were always to adjacent doorways. Initial and final heading angles were accurate (initial heading, visual: 11.7° ; final heading, visual: 2.8° ; initial heading, blindfold: 20.9° ; final heading, blindfold: 15.5°). Search and return times were also similar to those of control rats (search time, visual: 12.8 s; return time, visual: 3.3 s; search time, blindfold: 12.7 s; return time, blindfold: 4.8 s). Taken together with the above results, these data indicate that the impaired performance in the DTN-lesioned rats is unlikely to be due to collateral damage to the mlf.

Overall Comparisons Between ADN and DTN Lesions

By use of a mixed-design ANOVA (Lesion \times Condition), the analyses comparing ADN-lesioned, DTN-lesioned, and control

rats (collapsed across the two experiments) revealed several significant effects that indicate a more severe impairment in the DTN-lesioned rats relative to the ADN-lesioned rats. There was a main effect of lesion and condition for several of the measures: percentage correct, lesion, $F(2,31) = 41.24, p < .001$, condition, $F(1,31) = 8.87, p < .01$; final heading, lesion, $F(2,30) = 36.29, p < .001$, condition, $F(1,30) = 4.47, p < .05$; search time, lesion, $F(2,30) = 3.51, p < .05$, condition, $F(1,30) = 6.24, p < .05$; and return time, lesion, $F(2,30) = 9.98, p < .01$, condition, $F(1,30) = 8.42, p < .01$. The initial heading measure showed a main effect of lesion, $F(2,30) = 64.21, p < .001$, but not condition, $F(1,30) = 1.48, ns$. Although there was a significant Lesion \times Condition interaction for initial heading, $F(2,30) = 3.55, p < .05$, there was none for percentage correct, $F(2,31) = 0.447, ns$, or final heading, $F(2,30) = 1.27, ns$.

Post hoc tests for the percentage of correct returns to the refuge in both the visual and blindfold conditions indicated that control rats performed significantly better than both ADN- and DTN-lesioned rats and that ADN-lesioned rats performed significantly better than DTN-lesioned rats. Analyses revealed a similar pattern for the initial and final heading measures: post hoc tests indicated that control rats performed significantly better than DTN-lesioned rats but not better than ADN-lesioned rats on the initial heading in the visual condition. In addition, ADN-lesioned rats performed better than DTN-lesioned rats on this measure. In the blindfold condition for initial heading, control rats performed significantly better than both ADN- and DTN-lesioned rats, and ADN-lesioned rats performed significantly better than DTN-lesioned rats. Post hoc tests revealed a similar pattern for the final heading measure, where control rats performed significantly better than DTN-lesioned rats in both the visual and blindfold conditions, but not better than ADN-lesioned rats in either condition; however, ADN-lesioned rats performed significantly better than DTN-lesioned rats on the final heading measure in both the visual and blindfold conditions.

In sum, DTN-lesioned rats were impaired more than ADN-lesioned rats, which in turn were only mildly impaired compared with control rats. Within lesion groups, DTN- and ADN-lesioned rats performed equally poorly on both the blindfold and visual conditions.

Discussion

The data from Experiment 1 showed that rats with ADN lesions were mildly impaired in their correct choice behavior relative to control rats in both the visual and blindfold versions of the food-carrying task (see Figure 4). Analyses of the return paths also revealed a significant difference in both the initial and final headings of the ADN-lesioned rats relative to control rats in the blindfold (path integration) and visual versions of the task (see Figure 6). These data suggest that the ADN and, possibly more specifically, HD cells within the ADN play an important role in mediating both path integration and piloting.

The results of Experiment 2 showed that rats with DTN lesions were severely impaired in both visual and blindfold versions and were more impaired than ADN-lesioned rats. If angular path integration depends on HD cell activity, then the difference in performance between the two lesion groups implies that some compensatory strategy is available following ADN lesions but is

not fully preserved following DTN lesions. DTN lesions eliminate HD cell activity in the ADN (Bassett & Taube, 2001a) and presumably in the LMN and postsubiculum as well. Apparently, preventing HD cell information from flowing through the LMN \rightarrow ADN \rightarrow postsubiculum \rightarrow LMN loop is more detrimental in terms of path integration performance than disrupting the loop at one node (i.e., ADN). On the other hand, HD cell activity could still be present in LMN following ADN lesions. This possibility implies, however, that HD cell activity in LMN has behavioral relevance without being passed on to ADN. Therefore, the difference in behavioral outcome between ADN- and DTN-lesioned rats must rely on one or more alternate pathways for information from LMN or DTN, besides the LMN \rightarrow ADN projection. What this pathway might be is not clear. Except for some nearby areas within the hypothalamus, the LMN has few projections to areas other than ADN and DTN. Thus, the critical pathway may be DTN projections to areas other than LMN. Another major projection of the DTN is to the interpeduncular nucleus (Contestabile & Flumerfelt, 1981; Groenewegen & van Dijk, 1984), a brain area whose functional significance is not clear but has not been considered to play a major role in processing spatial information (reviewed in Morley, 1986). The interpeduncular nucleus has extensive connections with the habenula, but again, very little is known functionally about this area in terms of processing spatial information (Sutherland, 1982). Using *Phaseolus vulgaris*-leucoagglutinin as an anterograde tracer and injecting it into DTN, Groenewegen & van Dijk (1984) reported labeling in over 15 other areas besides the interpeduncular nucleus and LMN, ranging from subcortical to cortical regions. Of particular interest are the nucleus prepositus, an area medial to the parabrachial nucleus, and some ill-defined brainstem areas, including the peripeduncular region. Any of these areas could theoretically form components of a circuit that may be integral for path integration.

Cognitive Processes Involved in Path Integration

Although the computations involved in path integration may be performed in a single computation, its application during navigation involves a number of subcomponents. Accurate navigation first entails sensing one's current spatial orientation with respect to the environment, including one's location and directional heading. Second, a spatial analysis is required that computes a path from the current location to the desired goal. Third, given the animal's current directional heading, it then needs to compute the angular distance it must turn in order to embark on the right trajectory to the goal. Finally, some notion of the expected travel distance is usually encoded in the navigational plan. Where in the brain each of these events takes place is unclear. Some studies have argued for a neocortical locus (Recce & Harris, 1996; Save & Moghaddam, 1996), whereas others have placed these functions in the hippocampus (Golob & Taube, 1999; McNaughton et al., 1996; Whishaw & Maaswinkel, 1998). Similarly, where in the brain path integration mechanisms become integrated with landmark information is also unknown, although on the basis of known anatomy and physiology, Taube (1998) postulated that the ADN and postsubiculum are two candidate areas. Despite these uncertainties, our findings suggest that it is unlikely that the ADN plays a pivotal role in path integration processes, since impairments on both versions of the task were only mild. This finding is consistent with

other studies that have employed small discrete lesions of the anterior thalamus and generally found limited impairments on spatial tasks, including those that require the use of egocentric information (Aggleton et al., 1996; Sziklas & Petrides, 2004; Van Groen et al., 2002). It is possible that when lesions are confined to the ADN, other areas in the anterior thalamus (anteroventral and anteromedial) can compensate.

In contrast to ADN lesions, DTN lesions led to severe impairments in both versions of the task. The fact that DTN lesions impaired the piloting version, however, was unexpected, as much of the cognitive processing involved in landmark recognition and spatial orientation is believed to be managed by cortical structures (Janzen & van Turenout, 2004; Maguire, Frith, Burgess, Donnett, & O'Keefe, 1998; Taube, 1998). Given that the DTN is critical for direction-specific firing in the ADN (Bassett & Taube, 2001a), and most likely as well in the LMN and postsubiculum, it is possible that the deficits in the blindfold version with DTN lesions represent an impairment in processing the current spatial orientation of the animal. This explanation, however, would not explain the deficit we observed in the visual (piloting) version of the task because cortical pathways were left intact, and landmarks should have enabled the animal to update its orientation based on them. Alternatively, it is possible that the role of the DTN in processing spatial information is more fundamental, such that either it is critically important for navigational processes in general and not just path integration or path integration itself is fundamental for navigational processes, even when navigation involves piloting and the use of landmarks (Alyan & Jander, 1994, 1997; Etienne, 1992; Etienne, Teroni, Humi, & Portenier, 1990). Perhaps the animal cannot maintain a stable perception of its directional orientation, even in the presence of visual landmarks, because once its directional orientation is updated via landmarks, the system quickly drifts and becomes out of alignment due to dysfunctional path integration mechanisms as a result of a nonfunctional DTN. Thus, as soon as the animal's perceived orientation is updated, the system immediately becomes unstable, and the animal is disoriented again because an intact DTN is essential for maintaining the stability. This condition may arise because of drift in the preferred directions of HD cells resulting from an unstable attractor network, which similarly occurs following vestibular system interventions (Muir, Carey, Hirvonen, Minor, & Taube, 2004; Stackman & Taube, 1997). It is also possible that there may be a defective integrator and that the animal is unable to convert an angular head velocity signal to an angular head displacement signal. In these scenarios, the DTN would be important for navigation involving both path integration and landmarks. Still another possibility is that rats prefer to use path integration processes rather than piloting in this appetitive food-carrying task. Maybe a different outcome would have occurred if a similar task had been performed using aversive motivation, as rats often perform differently on tasks that appear to require the same skills but vary depending on whether appetitive or aversive motivation is used (Dudchenko, Goodridge, Seiterle, & Taube, 1997; Martin, Harley, Smith, Hoyles, & Hynes, 1997). This hypothesis could be addressed through testing of DTN-lesioned rats in an aversively motivated spatial task that required the use of landmarks.

Although the angle of their return paths showed no improvement at all, DTN-lesioned rats did improve in their ability to find the refuge, albeit slightly, over 3 days and were even above chance

on the first postlesion test day (Figure 8A). Thus, while their navigational abilities were impaired, other strategies and sources of information may have been available, including pathways that do not involve the DTN. Whether their first attempt was correct or not, rats often eventually found their way back to the refuge using a thigmotactic strategy, that is, approaching the wall at any angle relative to the refuge and then following the perimeter of the maze until they reached the correct exit. No attempt was made to block the bedding odor emanating from the refuge, and this odor may have provided an aid in identifying the correct exit once the rat was in its vicinity. Final headings were, on average, closer to the correct exit than initial headings, suggesting that the rats were able to correct their trajectory somewhat as they approached the wall. Whatever the other sources of information might have been, they were apparently not visual, as there was no significant difference between performances on visual versus blindfold conditions.

Processing Landmark Information

Compared with understanding where path integration information is processed, more is known about what brain areas process landmark information. Goodridge and Taube (1997) demonstrated that cells in the ADN maintain direction-specific firing following lesions of the postsubiculum, but the preferred firing directions of the ADN HD cells were no longer reliably controlled by a prominent visual landmark (i.e., cue card). Similarly, hippocampal place fields in postsubiculum-lesioned rats showed less landmark control than those in ADN-lesioned rats, again suggesting that HD cells in the ADN rely less on allothetic information than HD cells upstream in the postsubiculum (Calton et al., 2003). Results from functional imaging studies in humans suggest that the posterior parahippocampal area is activated for salient buildings and other objects that are used during landmark navigation (Aguirre, Detre, Alsop, & D'Esposito, 1996; Epstein, Graham, & Downing, 2003; Epstein & Kanwisher, 1998; Janzen & van Turennout, 2004; Maguire et al., 1998). The comparable area in rodents is the postrhinal cortex (Burwell, Witter, & Amaral, 1995), an area that has also been implicated in spatial processing in some studies (Bussey, Duck, Muir, & Aggleton, 2000; Liu & Bilkey, 2002) but not in others (Burwell, Saddoris, Bucci, & Wiig, 2004; Bussey, Muir, & Aggleton, 1999; Winters, Forwood, Cowell, Saksida, & Bussey, 2004). The absence of spatial deficits following lesions to this area in some studies may be attributed to the fact that animals may have been able to rely on idiothetic spatial information rather than on landmarks in the spatial tasks used. It is interesting that many of the postrhinal lesion studies that did not show a performance deficit in spatial tasks showed impairments in tasks involving the utilization of contextual information (Bucci, Phillips, & Burwell, 2000; Burwell et al., 2004) or object recognition (Winters et al., 2004)—processes that would be involved in landmark recognition. Taken together, these studies suggest that the rat postrhinal cortex may be involved in processing landmark information and would be consistent with the functions attributed to it from the human imaging studies. The postrhinal cortex projects directly to the subiculum and entorhinal cortex (Burwell & Amaral, 1998; Naber, Witter, & Lopes da Silva, 2001), which could, in turn, influence HD cells in the postsubiculum through projections from the subiculum (Van Groen & Wyss, 1990).

Our results suggest that an intact ADN is not critically important for processing landmark information. In contrast, an intact DTN appears critical for accurate navigation based on visual landmarks, even though this structure is several synapses removed from the cortical circuitry thought to be involved in processing landmark information. As discussed above, perhaps landmark navigation is partially dependent on path integration, and therefore, the DTN lesions disrupted performance under both visual and blindfold conditions. One final explanation for the finding that DTN lesions impaired navigation in the visual version of the task could be that DTN lesions caused a nonspecific effect (e.g., dizziness or general disorientation) that made it difficult to process visual cues accurately, resulting in impaired navigation.

Summary

In summary, rats with lesions of the ADN were only mildly impaired on a task that most likely required the use of path integration and on a version of the task in which they could select a route on the basis of visual landmarks. In contrast, lesions of the DTN produced much more profound impairments on both the path integration and visual landmark versions of the task. Taken together, these results suggest that the DTN, but not the ADN, is critical for accurate navigation on the basis of path integration or visual landmarks. Finally, because the impairments occurred on a previously acquired spatial task that was well learned, these results reflect a deficit in the utilization of spatial information rather than a spatial learning deficit.

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