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Medial septum lesions disrupt exploratory trip organization: Evidence for septohippocampal involvement in dead reckoning ☆

Megan M. Martin, Katharine L. Horn, Kelly J. Kusman, Douglas G. Wallace *

Psychology Department, Northern Illinois University, De Kalb, Illinois 60115-2892, USA

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Abstract

Rats organize their open field behavior into a series of exploratory trips focused around a central location or home base. In addition, differences in movement kinematics have been used to fractionate the exploratory trip into tour (i.e., sequences of linear movement or progressions punctuated by stops) and homeward (i.e., single progression direct to the home base) segments. The observation of these characteristics independent of environmental familiarity and visual cue availability has suggested a role for self-movement information or dead reckoning in organizing exploratory behavior. Although previous work has implicated a role for the septohippocampal system in dead reckoning based navigation, as of yet, no studies have investigated the contribution of the medial septum to dead reckoning. First, the present study examined the organization of exploratory behavior under dark and light conditions in control rats and rats receiving either electrolytic or sham medial septum lesions. Medial septum lesions produced a significant increase in homeward segment path circuity and variability of temporal pacing of linear speeds. Second, as an independent assessment of the effectiveness of the medial septum lesions, rats were trained to locate a hidden platform in the standard water maze procedure. Consistent with previous research, medial septum lesions attenuated learning the location of the hidden platform. These results demonstrate a role for the medial septum in organizing exploratory behavior and provide further support for the role of the septohippocampal system in dead reckoning based navigation.

Keywords: Path integration; Dead reckoning; Hippocampus; Acetylcholine; Movement organization; Idiothetic cues; Allothetic cues

1. Introduction

The behavior of rats in an open field is highly organized. Rats establish a home base and structure their movements around this location [1–7]. These movements have been characterized as a series of exploratory trips that are initially in close proximity to the home base then gradually expand into the environment [8]. The topographic and kinematic characteristics of exploratory trips have prompted dividing the trip into tour and homeward segments [9]. The tour segment begins at the home base, is a series of progressions (speeds above 0.1 m/s) punctuated by stops (speeds below 0.1 m/s), and concludes at the final stop. The homeward segment begins after the final stop, is a single progression, and ends as the rat arrives at the home base. Consistent temporal pacing of linear speeds (i.e., a monotonic increase to a peak located at the midpoint of the path followed by a monotonic decrease) is a kinematic characteristic unique to the homeward segment of the exploratory trip [10]. These different levels of exploratory behavior organization have been observed independent of allothetic cue availability and environmental familiarity, thereby supporting a role for self-movement information (i.e., vestibular, proprioception, or motor efferent copies), or dead reckoning based navigation [11], in guiding movement organization [9,12,10].

Damage to the hippocampal formation has been shown to disrupt exploratory trip organization [9,13]. Although rats with hippocampal lesions establish a home base and use that location to organize exploration, topographic and kinematic characteristics of the homeward segment are disrupted. The homeward segment is more circuitous, often restricted to the perimeter of the table, under light and dark testing conditions. Under dark conditions, rats with hippocampal lesions exhibit variable linear

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* Corresponding author. Tel.: +1 815 753 7071; fax: +1 815 753 8088.
E-mail address: dwallace@niu.edu (D.G. Wallace).

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speed temporal pacing, with the peak in speed occurring at various locations along the homeward segment. In contrast, the peak in speed consistently occurs in close proximity to the home base under light conditions. These disruptions in exploratory trip organization support a role for the hippocampus in dead reckoning based navigation [14, however see,15].

The present study examines the extent that the medial septum (the structure that provides major cholinergic inputs to the hippocampus) plays a role in the organization of exploratory behavior. Specifically, do animals with medial septum lesions establish home bases under dark and light conditions? Provided that home bases are established under both conditions, are the topographic and kinematic characteristics of tour and homeward segments intact? Considering that hippocampal lesions disrupt exploratory behavior organization, several lines of evidence suggest a role for the medial septum in organizing exploratory behavior. First, the medial septum provides a majority of the cholinergic and GABAergic projections to the hippocampus [16,17]. Second, damage to the medial septum has been shown to disrupt the electrophysiology of the hippocampus [18,19]. Finally, medial septum lesions have been shown to produce deficits on a variety of spatial tasks [20–26]. Although these lines of evidence predict that medial septum lesions should disrupt the organization of exploratory behavior, medial septum lesions spare many of the efferent and afferent connections compromised by hippocampal formation damage or fimbria-fornix transection. Therefore, intact systems may be sufficient to support the organization of exploratory behavior.

Exploratory behavior was examined in rats with electrolytic medial septum lesions, sham lesions, or un-operated controls. Rats were placed in a refuge that provided access to a circular open field and were free to explore first under dark conditions then under light conditions. Preference for the refuge was assessed under both conditions. Provided that rats established the refuge as a home base, the first eight exploratory trips that extended at least halfway across the open field were selected for analysis. To examine exploratory trip organization, trips were divided into tour progressions, homeward progressions, and stops. Several measures were used to quantify topographic (i.e., path length and path circuity) and kinematic (i.e., maximum speed and relative peak speed location) characteristics of each tour and homeward progression. Duration and change in heading direction were used to quantify stops during exploratory trips. Group differences in these measures provide evidence for the role of the medial septum in organizing exploratory behavior. Finally, as an independent assessment of the effectiveness of the medial septum lesions, rats were trained to locate a hidden platform in a standard water maze. Latency to reach the hidden platform, distance of the swimming path, and circuity of the swimming path were used to assess performance in the water maze.

2. Methods and materials

2.1. Animals

Subjects were 27 female Long-Evans hooded rats bred at Northern Illinois University from stock purchased from Harlan Sprague-Dawley. At the beginning of the experiment, rats weighed approximately 250 g. Rats were housed in groups of two or three in plastic cages in the colony room with the temperature maintained at 20–21 °C with a 12/12 h light/dark cycle. Thirteen rats received electrolytic lesions of the medial septum, seven received sham surgeries, and seven served as controls. All experimental procedures in this study were approved by the local Institutional Animal Care and Use Committee (IACUC), which follows the standards set by the National Institutes of Health.

2.2. Surgery

Electrolytic and sham subjects were anesthetized with a mixture of isoflurane and oxygen during surgery. Electrolytic lesions of the medial septum were produced by passing a 3.0 mA anodal current for 15 s through an electrode insulated except for 1.0 mm at its tip. There was a single lesion site on the midline, using coordinates relative to bregma and the surface of the dura: 0.5 mm anterior, 0.0 mm lateral, and 6.0 mm ventral [27]. Sham-operated controls were treated the same except that the electrode was lowered 3.0 mm below the skull surface without passing the current through the electrode. Rats were given a week to recover prior to testing.

2.3. Apparatus

2.3.1. Exploratory table

Rat exploratory behavior was examined on a wooden circular table (210 cm in diameter) without walls positioned approximately 83 cm above the floor. The table was painted white and located in a large room with a variety of cues (chair, door, two posters, and thermostat) available when lights were on. A small box (17×26×12 cm) with an oval hole (7 cm in diameter) in one of the sides was placed on the edge of the table serving as a refuge for the rat. To minimize the use of odor cues, the table was wiped down after each rat was tested and the table was rotated daily. The testing room was light proof, such that when the lights were turned off during dark testing, the room was completely dark. An infrared bullet camera was positioned perpendicular to the table. Three infrared emitter banks provided sufficient infrared illumination in the room such that the rat and testing apparatus were visible on the camera under dark conditions. The experimenter used an infrared spotter to test the animal under complete dark conditions. Infrared is a wavelength that the rat is not able to detect [28].

2.3.2. Water maze

The water maze was a circular galvanized steel tub (diameter 170 cm; height 60 cm) half-filled with water (~22 °C) made opaque by the addition of a 16 oz jar of white tempura paint. The placement of the tub in the room remained the same from day to day to maintain constant distal spatial cues (door, sink, poster, and cabinets) throughout all swim sessions. The hidden platform was located just below the surface of the water and was covered with a white athletic sock to provide purchase for the

rat. A bullet camera was mounted on the ceiling positioned perpendicular to the water maze.

2.4. Procedures

2.4.1. Exploratory testing

During exploration, rats were individually removed from the colony room and transported to the testing room. During transportation, the rat was rotated several times by the experimenter and transported via a circuitous path that varied from day to day, thereby disrupting the sense of direction in relation to the testing room. After the experimenter entered the testing room, the rat was placed in or near the refuge. The refuge was located at one of four quadrant positions, which varied across rats and remained stable for the duration of the experiment. Each exploratory session was 90 min in duration in which the animal was free to move around the table. On the first day of dark testing, the room was novel. Dark exploratory sessions continued until at least eight trips were collected from each rat. A single exploratory trip was defined as a departure from the refuge during which locomotor activity on the table displaced the animal at least halfway across the table and ending when the rat returned to the refuge (see Fig. 1). This requirement for an exploratory trip eliminates exploratory behavior that would be classified as lingering close to the home base [4]. After dark testing, rat exploratory behavior was examined under light conditions in the same room. Rats were allowed up to 10 sessions for a condition (dark or light) to complete eight exploratory trips. Sessions for a single rat were separated by at least 48 h. One rat that received an electrolytic medial septum lesion failed to meet the criteria under both conditions and was excluded from the study. One sham rat was excluded from the study due to experimenter error during recoding sessions. In addition, eight rats (4 electrolytic, 2 sham, and 2 control) were excluded from light exploration analyses after not fulfilling this criterion under light conditions. Table 1 indicates the number of rats from each group included for the analysis of the behavioral data.

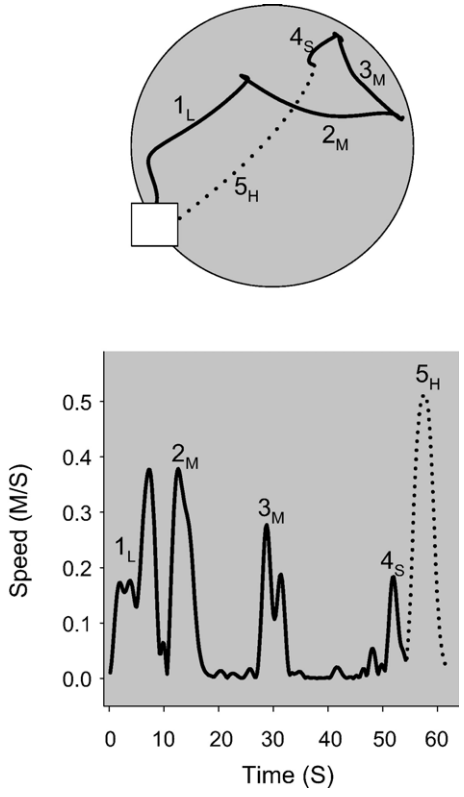

Fig. 1. Topographic (top panel) and kinematic (bottom panel) characteristics are plotted for a single exploratory trip under dark conditions. Tour progressions (bold line) and the homeward progression (dotted line) are numbered to indicate the sequence of movement. Subscripts indicate progression class: short (S), medium (M), long (L), or homeward (H) progression.

Table 1
Number of rats included in the analysis for each behavior test

Behavioral test	Medial septum	Sham	Control
Dark exploration	$n=12$	$n=6$	$n=7$
Light exploration	$n=8$	$n=4$	$n=5$
Water maze	$n=8$	$n=4$	$n=5$

2.4.2. Water maze testing

Rats that completed dark and light exploration were tested in the water maze. During acquisition training, rats were given two trials per day for ten days to locate the hidden platform. For each trial, a rat was released from one of four cardinal compass directions with its head facing the wall. Rats were given 60 s to reach the hidden platform. When the rat found the platform, it was left there for 30 s. If the rat failed to locate the hidden platform within 60 s, then the experimenter gently guided the rat to the platform and allowed the rat to remain on the platform for 30 s. After each trial, the rat was placed in a cage with dry paper towels until it was dry enough to be returned to its home cage. In addition, the water maze was strained of feces and gently stirred with a strainer to disrupt any scent left behind from the previous trial [29]. All rats were given their first trial prior to beginning any second trials. Although the release location varied across trials and days, the hidden platform remained stable throughout the ten days of acquisition training.

2.5. Behavioral analysis

2.5.1. General exploratory behavior

Ethovision video tracking system (Noldus Information Technology, Leesburg, VA) was used to quantify general characteristics of exploratory behavior. First, home base behavior was quantified by examining each animal's preference for the quadrant in which the refuge was located. The arena area was divided into four quadrants, and the time spent in each quadrant was calculated for the first 45 min of each rat's first day with exploratory trips. Time spent in each quadrant was used to calculate a modified version of Brown's mean search difference score [30]. Specifically, this score reflects the average difference between the percentage of time spent in each of the three non-target zones ($Z1$, $Z2$, and $Z3$) relative to the percentage of time spent in the target quadrant (T) containing the refuge: $[(T-Z1)+(T-Z2)+(T-Z3)]/3$. Quadrant preference values of −33 to zero

were associated with a preference for a quadrant in which the refuge was not located or equal preferences among quadrants, respectively. Preference for the quadrant in which the refuge was located was indexed by values greater than zero. Second, the total distance traveled was calculated for the same time frame.

2.5.2. Exploratory trip organization

The first eight exploratory trips that extended at least halfway across the table were selected for topographic and kinematic analyses. Exploratory trips were converted from analog recordings to a digital computer file via the Peak Performance system (Peak Performance Ltd., Englewood, CO) at a 30 Hz sampling rate. Exploratory trips were digitized by manually tracking a single point on the animal's body (the middle of the back at the level of the forelimbs) every fifth frame of digitized video (resulting in 6 samples per second).

Exploratory trips were divided into tour and homeward segments. Tour segments were defined as the portion of the path linking the initial departure from the refuge to the last stop made prior to returning to the refuge (see solid line in Fig. 1). The homeward segment was defined as the single progression that linked the last stop to the arrival at the refuge (see dotted line in Fig. 1). Stops were defined as periods of time ($\geq$0.67 s) in which movement did not exceed 0.1 m/s.

Exploratory trips were further divided into tour and homeward progressions. A progression corresponded to continuous periods of time in which speed exceeded 0.1 m/s. Therefore, the tour segment was characterized as a series of progressions punctuated by stops of varying duration. A rat's set of tour progressions from all eight exploratory trips was sorted based on travel distance from shortest to longest and divided into three classes: short, medium, or long. The homeward segment was a single progression and thus analyzed separately. Several measures were developed to examine group differences in topographic and kinematic characteristics of progression classes: average path length, average path circuity, average maximum speed, and the standard deviation of the relative peak speed location. First, path length was calculated from each progression's scaled *x*- and *y*-coordinates. Second, path circuity was calculated by determining the distance between the point where the progression started and the point where the progression ended and dividing that value by the distance that was actually traveled. Direct progressions through an environment are associated with path circuity values of 1.0 to 0.8. Paths restricted to the periphery of the table are associated with values of 0.7 to 0.6. Further decreases in path circuity values are associated with progressions becoming less direct. Third, maximum speed observed during the progression was recorded for each progression. Finally, the relative location of the peak speed was defined as the ratio between the distance from the start of the progression to the location of the peak speed and the overall distance of the progression. The standard deviation of relative location of the peak speed was calculated for each rat's class of exploratory trip progressions.

The duration of stops observed during each rat's set of eight exploratory trips were investigated under dark and light conditions. Stop durations were examined in association with the preceding progression's length. The length of the progression that preceded the stop was used to sort stops into three classes: stops after short progressions, stops after medium progressions, and stops after long progressions. The average stopping duration was calculated for each rat's stops observed after short, medium, and long progressions.

Change in heading direction during each stop was calculated by measuring the angle between successive progressions. The progression preceding a stop (P_1) was extended until it intersected with the current progression (P_2). The angle between the extended portion of P_1 and its intersection with P_2 was recorded as the change in heading direction. The value of change in heading ranged from 0 to 180, independent of left or right turns. Angles for heading direction were computed between successive progressions so that the last angle reflected the change in heading direction for the homeward progression.

2.5.3. Water maze

All swim sessions were videotaped for subsequent analyses. Ethovision video tracking system was used to collect data on latency to find the platform, swimming path distance and path circuity. Latency to find the platform was defined as the time required by the rat to locate the hidden platform after being placed into the water maze. The distance of the swim path was defined as distance swam until reaching the hidden platform. Swimming path circuity reflected the ratio between the distance between the point where the swim path started and the point where the swim path ended and the distance that was actually traveled. Average latency to find the platform, swim path distance, and swimming path circuity were calculated from each day's two trials. These measures were separately analyzed for acquisition.

2.6. Histology

Subsequent to behavioral testing, animals were deeply anesthetized and perfused with phosphate buffered saline followed by 4% paraformaldehyde in 0.1 M phosphate buffered picric acid. Brains were removed and stored in the 4% paraformaldehyde in 0.1 M phosphate buffered picric acid for two days at 4 °C. Brains were cut into 40 μm sections on a vibratome, and every third section was mounted on chromalum subbed slides. Slides were stained for acetylcholinesterase [31].

Coronal brain sections at the level of the dorsal hippocampus (approximately 3.3 mm posterior to bregma) and ventral hippocampus (approximately 5.2 mm posterior to bregma) from each rat were photographed with a color digital camera (Penguin 600 CL, Pixera Corporation, USA) attached to a microscope (Olympus BH2-RFCA, Olympus America Inc., USA). Color digital photographs were transformed into gray scale. Digital photographic files were opened with Scion Image for Windows (Scion Corporation, USA; freely available on the Internet at http://www.scioncorp.com). Average optical density values were obtained from a rectangular area (100 pixels × 300 pixels) in the hippocampus and cortex at the levels of the dorsal and ventral hippocampus. At the level of the dorsal hippocampus, the rectangular area sampled CA1, CA3, and DG regions of the

hippocampus, and the somatosensory and motor cortices of the cortex. At the level of the ventral hippocampus, the rectangular area sampled the CA1 region, although portions of the CA2 and CA3 regions were also taken. At the same level, the rectangular area sampled the secondary visual and parietal regions of the cortex. Optical density values are expressed as a function of the gray scale value (white: 0.0; black: 255).

3. Results

3.1. Histology

Photographs of acetylcholinesterase stained brain sections from representative control and medial septum rats at the level of the medial septum and dorsal hippocampus are located in the top and middle panels of Fig. 2. At the level of the medial septum, damage was restricted to the medial septum. Average optical density values for control, sham, and medial septum rats are plotted for dorsal hippocampus and the cortex at the same level in the bottom left hand panel of Fig. 2. The ANOVA conducted on dorsal hippocampal and cortical optical density values revealed significant main effects of brain area [$F(1,22)=7.241$, $p<0.05$], group [$F(2,22)=4.243$, $p<0.05$], and Group × Brain Area interaction [$F(2,22)=14.314$, $p<0.001$]. Control and sham groups had similar optical density values in both the dorsal hippocampus and the cortex, but the medial septum group had a significantly lower optical density value for the dorsal hippocampus than the control and sham groups (Tukey, $p<0.05$). The bottom right hand panel of Fig. 2 plots average optical densities for the ventral hippocampus and cortex at the level of the ventral hippocampus. The ANOVA conducted on ventral hippocampal and cortex revealed a significant Group × Brain Area interaction [$F(2,17)=5.619$, $p<0.05$]. The main effects for group [$F(2,17)=1.847$, $p=0.188$] and brain area [$F(1,17)=1.808$, $p=0.196$] were not significant. The medial septum group had significantly lower hippocampal optical density values relative to control and sham groups (Tukey, $p<0.05$). Medial septum lesions produced a decrease in acetylcholinesterase restricted to the dorsal and ventral extent of the hippocampus.

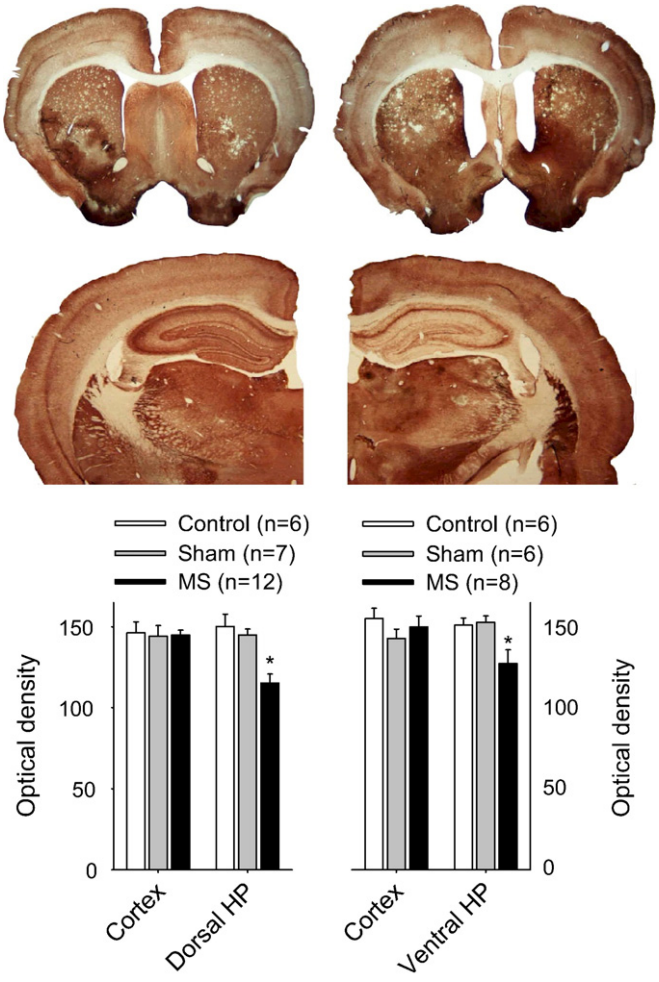

Fig. 2. Photographs of brain sections stained for acetylcholinesterase at the level of the medial septum (top panel) and dorsal hippocampal (middle panel) are from representative control (left hand panels) and medial septum (right hand panels) rats. Mean optical density values (+SE) are plotted for control, sham, and medial septum rats at the level of the dorsal (bottom left hand panel) and ventral (bottom right hand panel) hippocampus. Note: reductions in acetylcholinesterase staining associated with medial septum lesions are restricted to the hippocampus (*$p<0.05$).

3.2. General exploratory behavior

Initial analyses of general exploratory behavior examined differences between control, sham and medial septum groups' quadrant preferences and total travel distance. The ANOVAs conducted on quadrant preference scores did not reveal a significant effect of group under dark [$F(2,22)=0.251$, $p=0.780$] or light [$F(2,14)=0.050$, $p=0.951$] conditions. Similar analyses applied to measures of distance traveled did not reveal a significant effect of group under dark [$F(2,22)=0.902$, $p=0.420$] or light [$F(2,14)=0.969$, $p=0.403$] conditions. Observing preserved hippocampal acetylcholinesterase across control and sham groups in combination with an absence of differences in general exploratory behavior prompted collapsing across control and sham groups for all subsequent analyses. Analysis conducted on quadrant preference did not result in significant differences between groups under dark [$t(23)=0.656$, $p=0.518$] or light [$t(15)=-0.242$, $p=0.812$] conditions. Similarly, distance traveled did not significantly differ between groups under dark [$t(23)=-1.23$, $p=0.231$] or light [$t(15)=-1.384$, $p=0.187$] conditions. Both control and medial septum rats set up home bases in the quadrant with the refuge and traveled similar distances under dark and light conditions.

3.3. Exploratory trip organization

Fig. 3 plots the eight tour (top panels) and homeward (bottom panels) segments under dark conditions for a representative control (left panels) and medial septum (right panels) rat. Both rats' tour segments are not restricted to the periphery, rather they cover large portions of the testing area. In addition, homeward segments originate at different points throughout the environment.

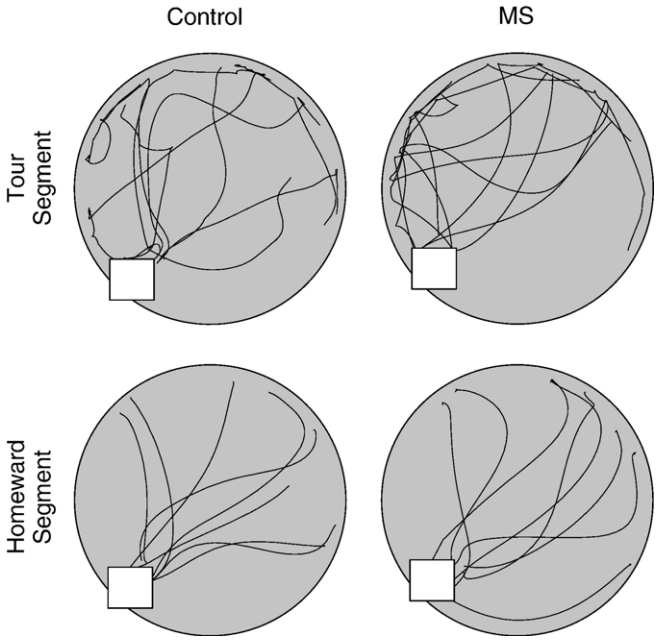

Fig. 3. Eight exploratory trips are plotted from representative control (left hand panels) and medial septum (right hand panels) rats. Tour (top panels) and homeward (bottom panels) segments are plotted separately. The white square indicates the location of the home base.

Several measures characterized the topography associated with exploratory tour and homeward progressions. The left hand panels of Fig. 4 plot the mean distance associated with short, medium, and long tour progressions from control and medial septum groups under dark (top panel) and light (bottom panel) conditions. The ANOVAs conducted on distances from each class of tour progression revealed a significant effect of progression class under dark [$F(2,46)=262.577$, $p<0.001$] and light [$F(2,30)=160.965$, $p<0.001$] conditions. The main effect of group and the Group × Progression Class interaction were not found to be significant under either testing condition. The right hand panels of Fig. 4 plot the average distances of homeward progression under dark (top panel) and light (bottom panel) conditions. Groups did not differ in the distances associated with homeward progressions under dark [$t(23)=-.462$, $p=0.649$] or light [$t(15)=-1.537$, $p=0.145$] conditions. Groups displayed equivalent distances for each class of exploratory trip progressions.

Left hand panels of Fig. 5 plot the average path circuity values for each class of tour progression under dark (top panel) and light (bottom panel) conditions. The ANOVAs conducted on path circuity values from each class of tour progression revealed a significant effect of progression class under dark [$F(2,46)=48.614$, $p<0.001$] and light [$F(2,30)=16.090$, $p<0.001$] conditions. The main effect of group and the Group × Progression Class interaction were not found to be significant under either testing condition. Average homeward progression path circuity values under dark (top panel) and light (bottom panel) conditions are plotted in the right hand panels of Fig. 5. Analysis of homeward progression path circuity values revealed that the medial septum group's homeward progressions were significantly more circuitous under dark [$t(23)=2.253$, $p<0.05$] and light [$t(15)=2.584$, $p<0.05$] conditions

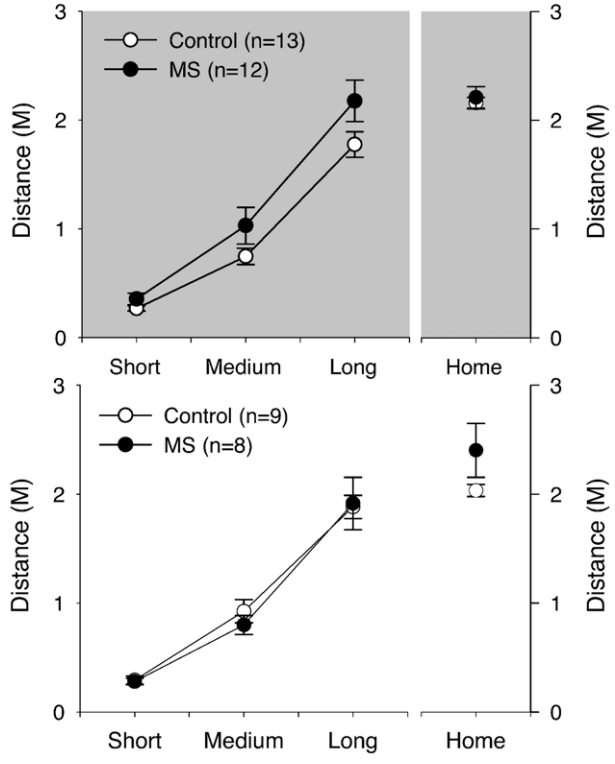

Fig. 4. Mean distances (±SE) associated with each class of progression are plotted for both groups under dark (top panels) and light (bottom panels) conditions.

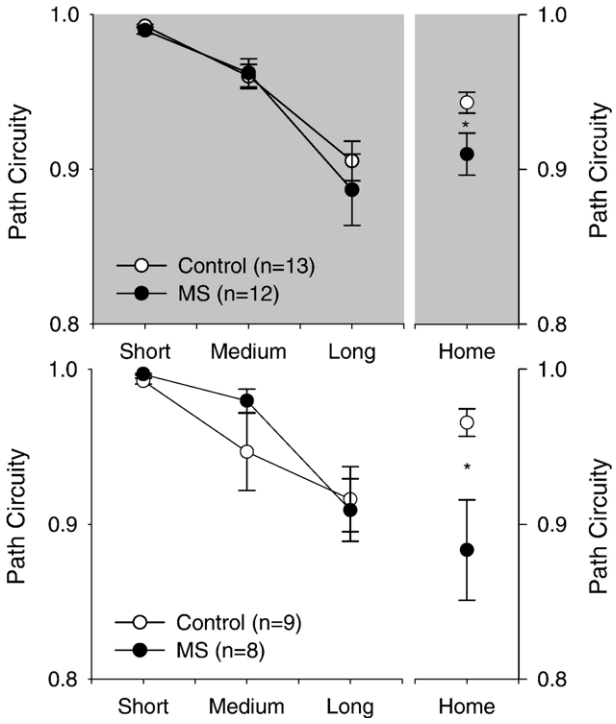

Fig. 5. Mean path circuity values (±SE) associated with each class of progression are plotted for both groups under dark (top panels) and light (bottom panels) conditions (*$p<0.05$).

relative to controls. Although no group differences in path circuity values were observed on tour segment progressions, medial septum lesions produced a small yet significant increase in homeward progression path circuity under dark and light conditions.

Fig. 6 plots linear speeds of normalized long tour (left hand panels) and homeward (right hand panels) progressions from a representative control (top panels) and a medal septum (bottom panels) rat under dark conditions. The control rat's homeward paths are associated with a consistent temporal pacing (i.e., monotonically increasing to a maximum speed followed by a monotonic decrease in speed) in contrast to that observed on long tour progressions. Differences in temporal pacing between long tour and homeward progressions were not observed in the medial septum rat.

Several measures characterized the kinematics associated with exploratory tour and homeward progressions. The left hand panels of Fig. 7 plot control and medial septum mean maximum speeds associated with tour progression classes under dark (top panel) and light (bottom panel) conditions. The ANOVAs conducted on maximum speeds from each class of tour progression revealed a significant effect of progression class under dark [$F(2,46)=200.381$, $p<0.001$] and light [$F(2,30)=115.835$, $p<0.001$] conditions. The main effect of group and the Group × Progression Class interaction were not found to be significant under either testing condition. The right hand panels of Fig. 7 plot the average maximum speeds of the homeward progressions under dark (top panel) and light (bottom panel) conditions. Groups did not differ in the maximum speeds associated with homeward progressions under dark [$t(23)=-.462$, $p=0.649$] or light [$t(15)=-1.537$, $p=0.145$] conditions. Both groups displayed similar maximum speeds for each class of exploratory trip progressions.

The relative peak speed location measure was developed to quantify differences in temporal pacing observed between tour and homeward progressions. The left hand panels of Fig. 8 plot control and medial septum mean standard deviation of relative peak speed locations for short, medium, and long tour progression classes under dark (top panel) and light (bottom panel) conditions. The ANOVAs conducted on relative peak speed location standard deviation from each class of tour progression revealed a significant effect of progression class under dark [$F(2,46)=45.370$, $p<0.001$] and light [$F(2,30)=15.046$, $p<0.001$] conditions. The main effect of group and the Group × Progression Class interaction were not found to be significant under either testing condition. The right hand panels of Fig. 8 plot the average standard deviation in relative peak speed locations for homeward progressions under dark (top

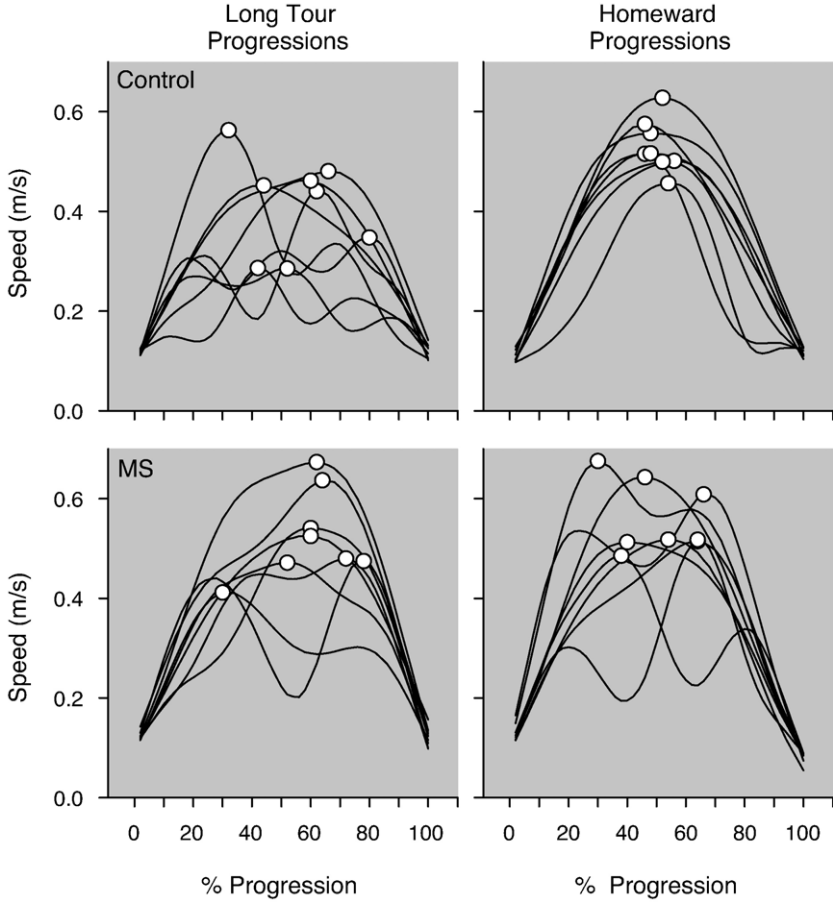

Fig. 6. Linear speeds are plotted for normalized long tour (left hand panels) and homeward progressions (right hand panels) from representative control and medial septum rats. Open dots represent the location of the peak speed for each progression. Note: The control rat exhibits consistent temporal pacing of linear speeds only on homeward progressions; whereas variable temporal pacing of linear speeds was observed on both types of progressions from the medial septum rat.

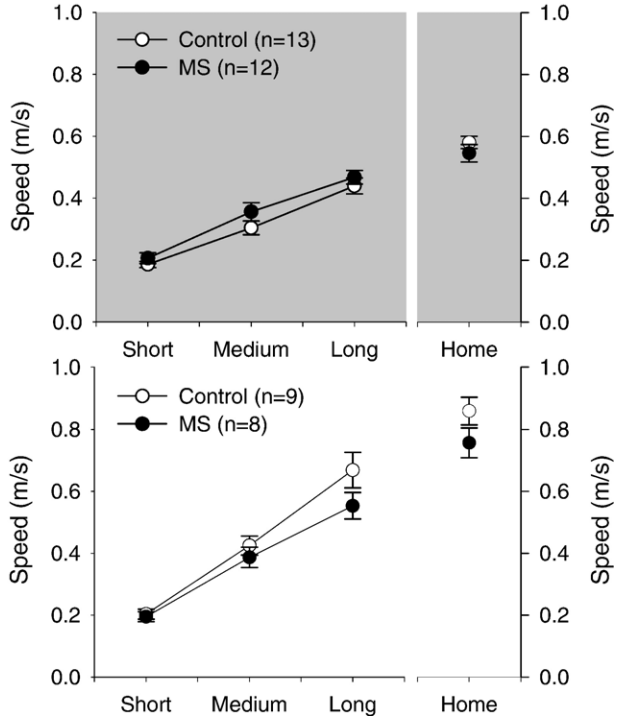

Fig. 7. Mean maximum speeds (±SE) associated with each class of progression are plotted for both groups under dark (top panels) and light (bottom panels) conditions.

panel) and light (bottom panel) conditions. The medial septum rats' average standard deviation in relative peak speed location was significantly more variable under dark [$t(23)=-5.105$, $p<0.001$] and light [$t(15)=-2.564$, $p<0.05$] conditions, relative to control rats. Groups did not differ in the variability of temporal pacing observed on short, medium, and long tour progression classes; however, medial septum lesions produced an increase in the variability of temporal pacing associated with the homeward progression under both dark and light conditions, relative to controls.

The duration of stops observed during the tour segment was analyzed according to the length of the preceding progression. Fig. 9 plots each groups average stop duration under dark (left hand panel) and light (right hand panel) conditions. The ANOVA conducted on each class of stops under dark conditions revealed a significant effect of stop class [$F(2,46)=17.957$, $p<0.001$] and group [$F(1,23)=11.491$, $p<0.005$]; however, the Group × Stop Class interaction was not significant [$F(2,46)=2.399$, $p=0.102$]. The trend analysis conducted on stop classes revealed a significant linear trend [$F(1,23)=33.165$, $p<0.001$]. The ANOVA conducted on each class of stops under light conditions did not result in a significant main effect of stop class [$F(2,30)=2.337$, $p=0.114$], group [$F(1,15)=0.946$, $p=0.346$], or Group × Stop Class interaction [$F(2,30)=0.024$, $p=0.976$]. Although both groups demonstrated increased stop durations after longer progressions under dark conditions, the medial septum group's stop durations were significantly shorter in duration. These effects were not observed under light conditions.

Finally, the average change in heading direction associated with stops during the tour segment and final stop prior to the homeward segment are plotted for both groups in Fig. 10. The ANOVA conducted on average change in heading directions under dark conditions revealed a significant main effect of segment [$F(1,23)=43.875$, $p<0.001$]. The main effect of group [$F(1,23)=0.456$, $p=0.506$] and Group × Segment interaction [$F(1,23)=2.041$, $p=0.167$] were not significant. Average change in heading direction associated with the stop prior to the homeward segments was significantly larger than that observed during the tour segment. Similar results were obtained under light conditions. The ANOVA conducted on average change in heading direction under light conditions revealed a significant main effect of segment [$F(1,15)=42.989$, $p<0.001$]. The main effect of group [$F(1,15)=0.350$, $p=0.563$] and Group × Segment interaction [$F(1, 15)=0.551$, $p=0.469$] were not significant. Under both conditions, changes in heading direction associated with the last stop were larger relative to stops during the tour segment.

To further investigate these differences, a secondary analysis was conducted using the average change in heading direction associated with the first (tour) and last (homeward) stops. The ANOVA conducted on changes in heading direction under dark conditions revealed a significant main effect of segment [$F(1,23)=24.134$, $p<0.001$]. The main effect of group [$F(1,23)=0.460$, $p=0.504$] and Group × Segment interaction [$F(1,23)=1.580$, $p=0.221$] were not significant. The ANOVA conducted on changes in heading direction under light conditions resulted in a significant main effect of segment

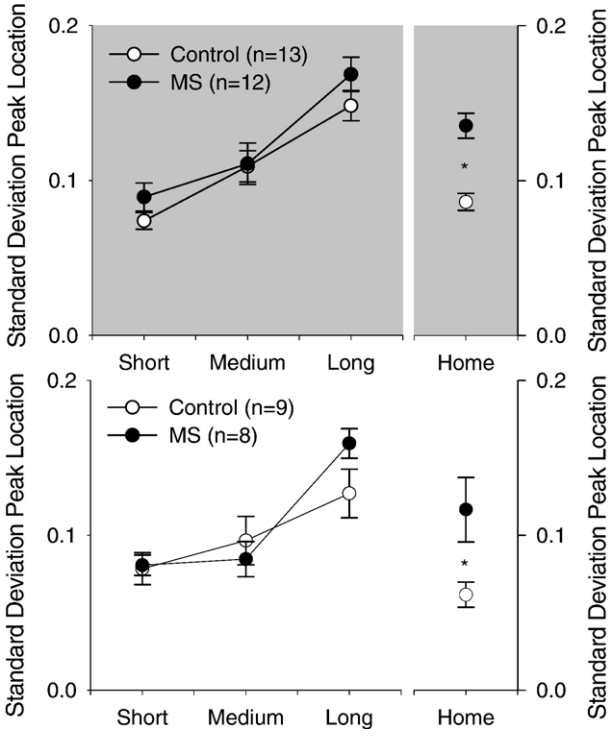

Fig. 8. Mean standard deviations of relative peak speed location (±SE) associated with each class of progression are plotted for both groups under dark (top panels) and light (bottom panels) conditions (*$p<0.05$).

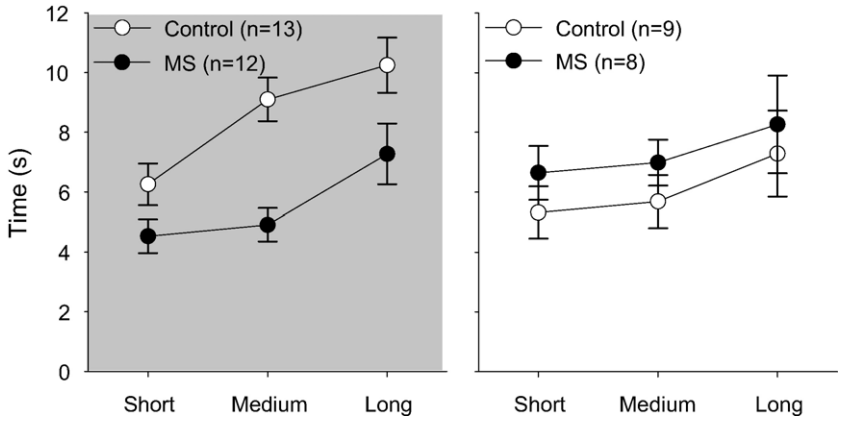

Fig. 9. Mean stop duration (±SE) subsequent to short, medium, and long progressions are plotted for both groups under dark (left hand panel) and light (right hand panel) conditions. Note: Control rats modify their stop duration as a function of progression length and testing condition.

[$F(1,15)=19.890$, $p<0.001$]. The main effect of group [$F(1,15)=0.034$, $p=0.857$] and Group × Segment interaction [$F(1,15)=2.461$, $p=0.138$] were not significant. Thus, the average change in heading direction for the homeward progression remained consistently larger than changes in heading during the tour for both groups when controlling for unequal samples.

3.4. Water maze performance

Performance in the water maze was indexed by the latency to locate the hidden platform, swimming path distance, and swimming path circuity. Fig. 11 plots control (top panels) and medial septum (bottom panels) rats' first swimming paths on day 1 (left hand panels) and day 10 (right hand panels). Although differences in swim paths are observed between day 1 and day 10, the medial septum rats' swim paths remain less direct, relative to control rats. The top panel of Fig. 12 plots each group's average latency to find the hidden platform during training. Although the ANOVA conducted on daily latencies revealed a significant main effect of days [$F(9,135)=20.388$, $p<0.001$], the group effect only approached significance [$F(1,15)=4.375$, $p=0.054$] and the Group × Days interaction was not significant [$F(9,135)=1.624$, $p=0.114$]. The trend analysis conducted across days revealed a significant linear trend [$F(1,15)=93.818$, $p<0.001$]. The middle panel of Fig. 12 plots distance traveled during training. The ANOVA conducted on swim path distances revealed significant main effects for day [$F(9,135)=17.932$, $p<0.001$] and group [$F(1,15)=5.179$, $p<0.05$], although the Group × Day interaction was not significant [$F(9,135)=1.541$, $p=0.140$]. The trend analysis conducted across days revealed a significant linear trend [$F(1,15)=81.329$, $p<0.001$]. The bottom panel of Fig. 12 plots each group's average swim path circuity during training. The ANOVA conducted on daily swimming path circuity values revealed significant main effects of days [$F(9,135)=8.029$, $p<0.001$] and group [$F(1,15)=6.618$, $p<0.05$]; however,

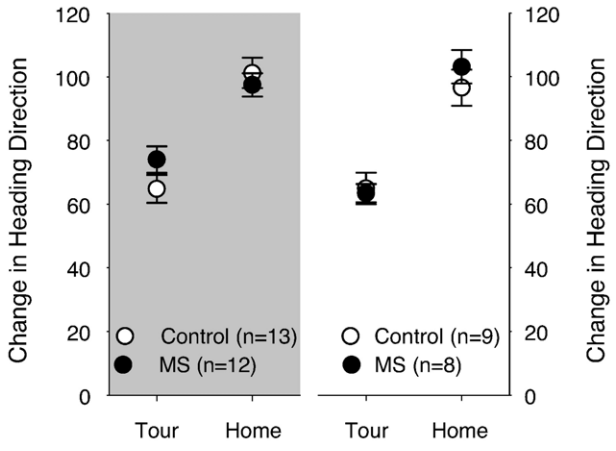

Fig. 10. Mean change in heading direction (±SE) between tour progressions and prior to returning home are plotted for both groups under dark (left hand panel) and light (right hand panel) conditions.

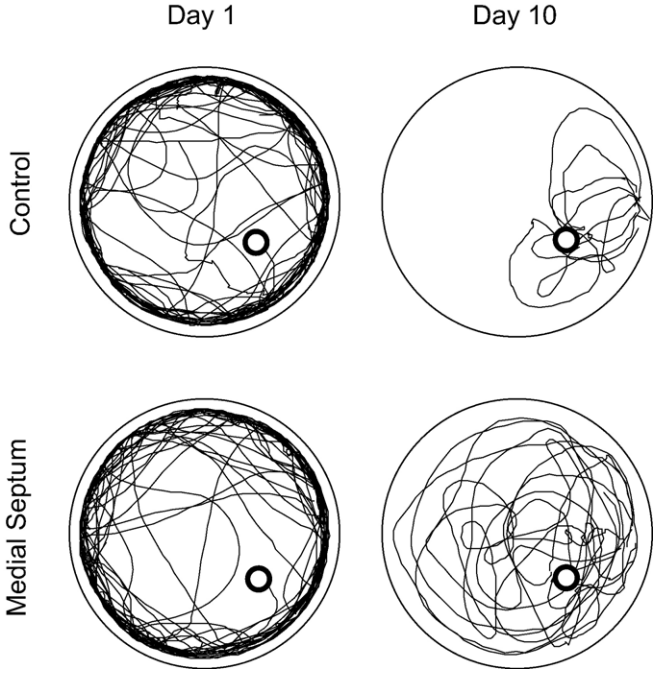

Fig. 11. Swimming paths for the first trial on day one (left hand panels) and day ten (right hand panels) of training are plotted for control and medial septum rats.

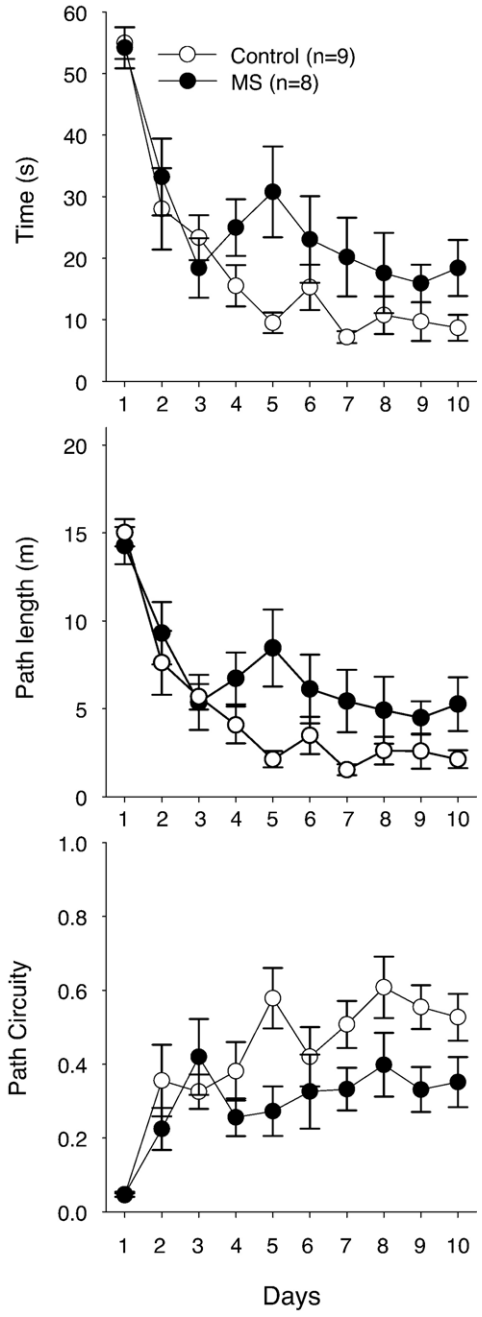

Fig. 12. Mean latency (±SE), path distance (±SE), and path circuity (±SE) are plotted in the top, middle, and bottom panels for both groups across the ten days of hidden platform training.

the Group × Days interaction [$F(9,135)=1.629$, $p=0.113$] was not found to be significant. The trend analysis conducted on daily swim path circuity values revealed a significant linear trend [$F(1,15)=26.643$, $p<0.001$]. In general, rats with medial septum lesions displayed impairments in learning the location of the hidden platform.

4. Discussion

The current study investigated the effects of medial septum lesions on the organization of exploratory behavior in an open field. Both medial septum and control groups adopted the refuge as a home base and organized their exploratory trips around this location; however, medial septum lesions disrupted specific components of exploratory trip organization. First, medial septum lesions produced a significant increase in the variability of temporal pacing restricted to the homeward progression. Second, a small yet significant increase in path circuity was observed only on homeward progressions in rats with medial septum lesions. Finally, the novel finding of a relationship between stop duration and the length of the preceding progression under dark conditions was compromised in rats with medial septum lesions. These disruptions demonstrate a role for the medial septum in organizing exploratory behavior and provide additional support for the involvement of the septohippocampal system in processing self-movement information related to dead reckoning based navigation.

Exploratory trip organization has been suggested to depend on dead reckoning based navigation [9]. Specifically, self-movement information generated on the tour segment is used to dead reckon or estimate the direction and distance to the home base. Observing exploratory trip organization independent of lighting condition and environmental familiarity has supported this claim [10]. Previous work has demonstrated that exploratory trip organization also depends on the hippocampal formation [9,13]. In particular, hippocampal lesions produced disruptions specific to the homeward segment. Although hippocampal lesions significantly increased circuity of the homeward segment under both light and dark conditions, differences in temporal pacing of linear speeds were observed between conditions. Under dark conditions, rats with hippocampal lesions displayed highly variable temporal pacing of linear speeds. In contrast, under light conditions, temporal pacing of linear speeds was consistent; however, the peak in speed shifted closer to the home base. These results are consistent with hippocampal lesions disrupting direction and distance estimation under dark conditions, yet sparing the ability to use landmarks in the environment (i.e., home base) for piloting. In the present study, medial septum lesions only produced a small, yet significant, increase in homeward segment path circuity and did not significantly influence the change in heading direction associated with the homeward segment. These results were observed independent of dark or light conditions; consistent with medial septum lesions at most producing only a mild deficit in estimating direction. In contrast, medial septum lesions significantly increased the variability of the temporal pacing of linear speeds under dark and light testing; consistent with medial septum lesions impairing distance estimation. One possible explanation for the differences in exploratory trip organization observed between medial septum lesions in the present study and hippocampal lesions previously reported is that there is a differential sparing of the ability to derive direction and distance estimates from self-movement information. Medial septum lesions impair estimates of distance yet spare estimates of direction; whereas, hippocampal lesions impair both estimates. Hippocampal rats use environmental landmarks to pilot, thereby compensating for the inability to derive direction and distance estimates from self-movement

information. In contrast, the ability of medial septum rats to derive estimates of direction from self-movement information may be sufficient to guide navigation under light conditions, and having this ability may not warrant the use of piloting as a compensatory mechanism for organizing exploratory behavior under light conditions. This interpretation is consistent with a role for dead reckoning in organizing exploratory behavior under dark and light conditions.

The novel finding that under dark conditions, control rats exhibited a systematic relationship between stop duration and preceding progression length may be related to processing of self-movement information during stops. Long progressions are associated with a larger informational load and, therefore, may require more processing time. The absence of this relationship under light conditions may be related to the availability of additional self-movement cues related to optic flow. Studies have demonstrated a role for optic flow in maintaining place field stability [32]. It is possible that access to optic flow may have reduced the informational load associated with longer progressions under light conditions. Interestingly, stop durations did not vary as a function of progression length or testing condition in rats with medial septum lesions. There are two possible explanations for this observed effect of medial septum lesions. First, animals with medial septum lesions may not have access to self-movement information generated on the preceding progression during stops; thereby, information load cannot vary as a function of progression length. Second, medial septum lesions may disrupt processes critical for deriving distance estimates from self-movement information. For example, medial septum lesions may impair evaluating linear speeds within the appropriate temporal context. In either case, the result is an impaired estimation of distance associated with the homeward segment. These results are consistent with processing of self-movement information during stops; however, it is not clear whether the disruption in the relationship between stop duration and preceding progression length is related to a lack of access to self-movement information or impairments in processes related to deriving distance estimates.

Electrophysiology studies have also supported a role for the medial septum in sensory processing. The medial septum has been shown to be critical for the generation of rhythmic slow-wave field potential, or theta rhythm (3–12 Hz), in the hippocampus [19]. Research suggests that there are two types of hippocampal theta. One type of hippocampal theta is associated with voluntary behaviors (e.g., walking, running, rearing) and is resistant to the administration of atropine [33]; whereas, a second type of hippocampal theta observed during periods of sensory processing while the rat is immobile has been shown to be attenuated by the administration of atropine [34]. This second type of hippocampal theta, or atropine sensitive theta, has been observed prior to the initiation of food protection behaviors, and intraseptal infusions of atropine attenuate these behaviors [35]. Magnitude of food protection behavior has been shown to depend on the rat's estimate of time required to consume the food item [36]. It is possible that atropine sensitive theta may reflect sensory processing related to generating estimates of temporal intervals used to guide the magnitude of food protection behaviors. An important parallel in the current study is that dead reckoning involves processing self-movement information within the appropriate temporal context to plot the correct distance and direction of the path back to the refuge. Therefore, disruption in self-movement information processing associated with medial septum lesions may reflect impairments in evaluating self-movement information within an appropriate temporal context.

The medial septum provides a majority of the cholinergic afferents to the hippocampal formation. The consistent relationship observed between markers of cholinergic function in the hippocampus and cognitive deficits in patients suffering from Alzheimer's Disease has prompted the development of the cholinergic hypothesis [37,38]. Studies using nonselective lesions of the medial septum consistently show impairments in a variety of spatial learning tasks, thereby supporting the cholinergic hypothesis [20–26]. The development of lesion techniques selective for cholinergic cells in the medial septum has provided a tool for investigating the role of hippocampal cholinergic afferents in spatial orientation [39]. Studies examining the effects of these selective lesion techniques have resulted in both impairments [40–46] and intact performance on a variety of spatial tasks [47–54]. Differences in performance on spatial tasks observed across lesion techniques have been attributed to the sparing of non-cholinergic neurons (GABAergic neurons) in the medial septum; however, performance was always assessed on tasks in which animals had access to both self-movement and environmental cues. The current study demonstrated that medial septum lesions produced disruptions in exploratory trip organization, consistent with impairments in processing self-movement information. In addition, impairments in learning the location of the hidden platform were associated with medial septum lesions. These observations support previous claims that self-movement information facilitates learning the relationships between environmental cues [55–58].

Although differences observed in the organization of exploratory trips are consistent with a role for the medial septum in processing self-movement information, several factors may have also contributed to group differences. First, animals may use olfactory cues associated with the home base or odor trails left on the table to organize exploratory behavior, suggesting that medial septum lesions impaired the rats' ability to use olfactory cues for navigation. This is unlikely because bulbectomized (anosmic) rats have been shown to establish a home base and use that location to organize exploratory behavior [12]. In addition, kinematic profiles of odor tracking behavior are qualitatively different from that observed during exploratory trips [13]. Therefore, odor cues do not appear to be a critical factor in the organization of exploratory trips. Second, medial septum lesions may have attenuated the tendency to establish a home base and use it to organize exploratory behavior. Both groups displayed equivalent preference for the quadrant in which the refuge was located under dark and light conditions. This observation suggests that the tendency to set up a home base and return to that location did not vary across groups. Third, medial septum lesions may have produced a

general change in locomotor activity [59]; however, this is unlikely for a number of reasons. Total distance traveled under dark and light conditions was similar across groups conflicting with the possibility that group differences were based on bradykinesia or hyperkinesia. In addition, groups did not vary in topographic or kinematic characteristics of tour progressions. These results discount the possibility of non-specific factors mediating group differences in exploratory trip organization. Finally, electrolytic medial septum lesions are non-specific. Damage as the result of the electrolytic lesions technique compromises cell bodies, afferents fibers, efferent fibers, and fibers of passage. In addition, the medial septum projects to the entorhinal and cingulate cortex. Therefore the behavior disruptions observed in the current study may depend on compromised function in any of these systems. Future studies using cell specific lesion techniques, indicated above, may provide insight to the role of these other structures in organizing exploratory behavior.

This study examined the effects of medial septum lesions on the organization of exploratory behavior in an open field. All rats in the current study adopted the refuge as their home base and used it to organize their exploratory behavior. Although topographic and kinematic characteristics of tour progressions did not vary between groups, rats with medial septum lesions displayed significantly more circuitous and more varied linear speed temporal pacing on homeward progressions. The novel observation of a systematic relationship between stop duration and length of the preceding progression suggests that processing of self-movement information generated on the tour segment may occur during stops. Therefore, disruptions in the relationship between stop duration and preceding progression length associated with medial septum lesions may be related to the impairments observed on the homeward progression. This study provides further evidence for a role of the septohippocampal system in processing self-movement information required for dead reckoning based navigation.

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